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A REPORT OF 549 CASES OF BREAST CANCER IN WOMEN 35 YEARS OF AGE OR YOUNGER

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THE PROGNOSIS of carcinoma of the breast in a young woman has been a controversial subject for decades. Conflicting opinions have been voiced concerning the influence of the age of the patient, and whether the course of the disease was more rapid and its response to treatment less favorable in the younger age groups. The significance of mammary carcinoma in a young woman simultaneous with pregnancy, or in the postpartum period, likewise has been debated in terms of survival. The interruption of pregnancy when breast cancer was concomitant has also been an unsettled issue. Lastly, what should the young woman, who has been treated for breast cancer, be told concerning the advisability of future pregnancies? The results of this study of 549 patients who were 35 years of age or younger may provide a plausible therapeutic approach to the problem.

In 1880, Samuel W. Gross said, "The rate of growth (of breast cancer) is not, contrary to the generally received opinion, influenced by the early age of the patient. . . . When, however, carcinoma appears during pregnancy or during lactation, its growth is wonderfully rapid and its course excessively malignant."

Burton J. Lee, in 1931, concluded in his study, "My associates and I have been more impressed year by year with the poor end results following radical surgical intervention in cases of cancer of the breast in young women."

Equally pessimistic concerning the prognosis of mammary carcinoma in younger patients was the report by Taylor.

Nathanson and Welch stated that "cancer of the breast in the hospital cases is more malignant in the young and less so in the old."

James Ewing, in 1940, commented that "before 30 years of age mammary cancer is extremely fatal so that some surgeons prefer not to operate during this period."

In 1943, de Cholnoky collected from 5 major institutions in New York City 73 cases of breast cancer in women under the age of 30 years and reviewed the literature dating back to 1851. He reported a 40.8 per cent 5 year survival, and a 37 per cent 10 year survival in the surgically treated patients within these age limits.

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TABLE I.—CLINICAL CLASSIFICATION

	Unassociated with pregnancy	*Pregnant (concurrent or subsequent)*	*Totals*
Primary operable	279	50	329
Operable after local excision	50	19	69
Recurrent operable	15	5	20
Total operable	344	74	418
Primary inoperable	26	13	39
Recurrent inoperable	48	14	62
Total Inoperable	74	27	101
Prophylactic*	23	7	30
Grand total	441	108	549

*See footnote on this page.

TABLE II.—FAMILY HISTORY IN 498 PATIENTS

	No.	*Per cent*
Negative for cancer (all types)	382	77.0
Positive for cancer (all types)	116	23.0
Positive for breast cancer	51	10.0
Breast cancer in mother	25	5.0
Breast cancer in sister	12	2.4
Positive for cancer	116	
Positive for breast cancer	51	35.0
Breast cancer in mother	25	21.5
Breast cancer in sister	12	10.3
Positive for breast cancer	51	
Positive in mother	25	49.0
Positive in sister	12	23.5
Positive in all others (aunts, grandmothers, etc.)	14	27.4

MacDonald, in 1956, noted the remarkable variation of opinion relating to the prognosis of breast cancer in young women and cited a number of references which attested to this lack of unanimous feeling. He reviewed the records of 7 major hospitals in the Los Angeles area and accumulated 55 cases in women below the age of 30 years. His evaluation of the results of therapy suggested that the course of breast cancer in young women was no different from other age groups with the exception perhaps of the extremely elderly patient.

A further review of the literature has suggested that breast cancer concurrent with pregnancy may offer a very poor prognosis.

Westberg, in a comprehensive analysis, concluded with: "It would thus seem that the pregnancy has no very great effect on the prognosis of breast cancer apart from the fact that the patients delay in consulting a doctor, and that the doctor is inclined to postpone the surgery."

MATERIAL

Five hundred and forty-nine cases of histologically proved breast cancer in patients 35 years of age or younger were seen at Memorial Center from 1937 through 1949. The study was limited by the year 1949 so that all patients would have a minimum follow-up period of 5 years from the date of admission. Sarcomas of the breast have been excluded. The average number of patients seen yearly in this age group was 42, or about 3 to 4 per month.

TABLE III.—MULTIPLE PRIMARY NEOPLASMS

	No.
Prior	2
Reticulum cell sarcoma	1
Carcinoma of the cervix	1
Concurrent	2
Rectal carcinoma	1
Carcinoma of the cervix	1
Subsequent	4
Carcinoma of the fundus	1
Bilateral papillary and solid adenocarcinoma of the ovaries	1
Mixed tumor of parotid	1
Chondrosarcoma of the mandible	1
Total	8

Each patient was assigned to one of the following clinical categories based on the history and physical findings at the time of admission: (1) primary operable breast cancer; (2) operable breast cancer after local excision; (3) recurrent operable breast cancer; (4) prophylactic breast cancer[1]; (5) primary inoperable breast cancer; (6) recurrent inoperable breast cancer. Of the 549 patients seen, 418 presented an operable setting. One hundred and one patients were inoperable. Thirty patients (prophylactic[1] group) had received adequate surgical treatment elsewhere and showed no clinical evidence of breast cancer at the time of admission. If the 30 prophylactic[1] patients are excluded, 418 patients (80 per cent) were operable and 101 patients (20 per cent) were inoperable. An 80 per cent operability rate is at least equal to, if not considerably better than that usually found in all age groups combined. The operability rate for all age groups at Memorial Center is between 66 and 70 per cent. The clinical categories and the number of patients in each group asso-

[1]Prophylactic breast cancer is the term applied herein to a group of patients admitted to the Breast Service of Memorial Hospital who had had a previous radical or simple mastectomy, not performed by the Breast Service and who, after their operation, were referred to the service without evidence of recurrent disease, either local or distant.

TABLE IV.—PREVIOUS GYNECOLOGIC SURGERY

Procedure	*Indication*	*No. patients*	*Age at surgery*
Hysterectomy	Unknown	3	28, 30, 31
Hysterectomy (1 case with bilateral oophorectomy)	Fibroids	7	21, 23, 25, 28, 30, 31, ?
Hysterectomy and bilateral oophorectomy	Cancer of cervix	1	32
Unilateral oophorectomy	Cyst	10	17, 20, 23, 24, 26, 26, 29, 29, 31, 34
Bilateral oophorectomy	Cysts	1	35
Unilateral oophorectomy	Ectopic pregnancy	3	18, 24, ?
Amputation cervix	Bifid cervix	1	23
Cervical polypectomy	Polyp	1	34
Uterine suspension	Retroversion	2	27, 30
Total		29	Median age, 26 years

TABLE V.—SUBSEQUENT GYNECOLOGIC SURGERY (NOT THERAPEUTIC FOR BREAST CANCER)

Procedure	*Indication*	*No. patients*	*Time*
Hysterectomy and bilateral oophorectomy	Bilateral papillary and solid adenocarcinoma ovaries (cause of death)	1	6 years after radical mastectomy
Hysterectomy and bilateral oophorectomy	Carcinoma of the fundus (cause of death)	1	10 years after radical mastectomy
Hysterectomy and bilateral oophorectomy	Fibroid uterus—bleeding	2	8 and 7 years after bilateral radical mastectomy
Cervical polypectomy	Polyp	1	8 years after radical mastectomy

ciated with pregnancy have been enumerated in Table I.

The distribution of the 549 patients by age was as follows: 19 to 25 years, 21 patients; 26 to 30 years, 124; 31 to 35 years, 404. The median age was 33 years.

Two hundred and fifty-two cases involved the right breast and 271 the left. Twenty-three cases were bilateral—of these, 21 were nonsimultaneous and 2 were simultaneous. Three patients had lesions too far advanced to determine the side of origin.

Pertinent facts relating to family history were not recorded in 51 cases—leaving 498 patients for evaluation (Table II). There was no family history of cancer of any type in 382 cases (77 per cent). A family history of cancer (all types) in blood relatives was found in 116 cases (23 per cent). In this latter group there was a familial history of breast cancer in 51 patients—about 10 per cent of all the evaluated cases. It should be noted that in the patients *with* a familial history of cancer, the breast was the organ involved in 35 per cent. In those patients with a familial history of breast cancer almost one-half reported breast cancer in the mother and almost one-fourth in a sister. In 4 of the 12 patients with breast cancer in a sister, it occurred before the age of 35 years.

Eight (1.4 per cent) of the 549 patients had multiple primary malignant neoplasms (excluding skin tumors) which were located elsewhere than in the breast (Table III).

Four hundred and forty-five patients (82 per cent) were married, and 104 patients (18 per cent) were single. One hundred and seventy-two patients (104 unwed and 68 married) gave no history of prior pregnancy, 34 per cent. The remaining 334 had been pregnant at least once, 66 per cent. Of the latter group 24 patients did not carry to term, 7.1 per cent. These figures indicated that breast cancer in the age group under study occurred with greater frequency in those patients who had had a previous pregnancy—an incidence of almost 2 to 1.

The incidence of previous gynecologic surgery was only 5.2 per cent, but additional gynecologic disorders were found on admission and also subsequent to treatment for breast cancer (Tables IV and V). A total of 48 patients had previous, concurrent, or subsequent gynecologic disorders. These included 2 cases of cancer of the cervix, 1 case of bilateral ovarian carcinoma, 1 of carcinoma of the fundus, 18 cases of uterine myomas, 14 of ovarian cysts, and 2 of cervical polyps.

The distribution and nature of initial symptoms in the primary operable group (329 patients) follows. A breast mass was dis-

TABLE VI.—NIPPLE DISCHARGE IN 18 PATIENTS

Pathologic condition	*Serous*	*Bloody*	*Unstated*
Infiltrating duct carcinoma	2	6	1
Papillary carcinoma	1	4	–
Comedocarcinoma	1	1	–
Paget's disease with inf. duct carcinoma	1	–	–
Lobular carcinoma in situ	–	1	–

TABLE VII.—SUMMARY OF PATHOLOGIC DIAGNOSIS IN 549 PATIENTS

	No. of patients
"Mammary carcinoma"	91
Infiltrating duct carcinoma	397
Grade 1, 1	
Grade 2, 170	
Grade 3, 161	
Grade 4, 3	
Ungraded, 62	
Medullary carcinoma	26
Papillary carcinoma	9
Noninfiltrating, 5	
Infiltrating, 3	
Intracystic, 1	
Comedocarcinoma	9
Infiltrating, 5	
Noninfiltrating, 4	
Colloid carcinoma	5
Paget's disease	5
With infiltrating duct carcinoma, 3	
With noninfiltrating duct carcinoma, 1	
With noninfiltrating comedocarcinoma, 1	
Lobular carcinoma	4
In situ, 3	
Infiltrating, 1	
Miscellaneous group	3
Gelatinous carcinoma, 1	
Squamous carcinoma, 1	
Spindle cell carcinoma, 1	

covered without medical assistance in 92 per cent of the patients. In only 1 per cent (3 patients) of the group was the tumor discovered on a routine physical examination.

Nipple discharge was present in 5.5 per cent (18 patients) and bloody discharge outnumbered serous discharge. The pathologic conditions present in those patients with nipple discharge have been noted in Table VI. Of interest is the fact that bloody nipple discharge more often indicated an infiltrating duct carcinoma with no papillary component. Nipple encrustation was noted by 4 patients, 1.2 per cent. Inversion of the nipple was found in 1 patient, .03 per cent. A history of trauma was reported by only 5 patients.

PATHOLOGY

A histologic diagnosis of carcinoma was obtained in each of the 549 patients (Table VII). "Mammary carcinoma" was reported in 91 instances. This diagnosis was usually based on aspiration biopsy of massive primary or recurrent lesions when it was only a confirmatory histologic diagnosis that was desired.

Five patients had 2 multicentric breast cancers, and 1 had 3 within the same breast. There were 3 patients with "inflammatory carcinoma," 1 of which was bilateral. All were classified as inoperable at the time of admission. None of the 3 patients had received previous therapy and each died within a period of 1 year.

FIVE YEAR CLINICAL CURE DATA

Total experience—unselected results. If all patients other than those known to be free of clinical evidence of recurrent or metastatic breast cancer 5 years after therapy were classified as failures, the lowest possible clinical cure rate was obtained. There were 169 patients clinically free of cancer at the 5 year mark, 30.7 per cent.

To simplify tabulation throughout the remainder of this report, the 30 patients in the "prophylactic" group will be included in the "operable" group unless otherwise indicated.

Selected results. In the operable group (448 patients) again 169 patients were clinically free of cancer for 5 years—a minimum clinical cure rate of 37.7 per cent. The only selection was the exclusion of the inoperable patients. If further selection were made in the operable group one could eliminate 32 patients who refused treatment, died of other causes, or were lost to follow-up within 5 years without evidence of recurrent or metastatic cancer. This provided 169 five year clinical cures out of 416 patients, a rate of 40.6 per cent, and the maximum percentage one could obtain from the recorded data. These clinical cure rates compare favorably with the rate for 13,000 patients of all ages reported from Memorial Center in 1949 (1). The clinical cure rate for the latter group based on total experience was 39.6 per cent.

VARIOUS INFLUENCES ON SURVIVAL RATE

The most adequate data relating to histologic confirmation of metastatic involvement of the axillary nodes were found in the previously untreated operable patients and in those who had had only local excision prior to admission, a total of 398 patients. Of these, microscopic proof of axillary node metastases was lacking in 31. There remained 367 patients evaluated as follows: positive nodes in 271 patients (59.1 per cent) and 5 year clinical cure in 46 patients (21 per cent); negative nodes in 150 patients (40.8 per cent) and 5 year clinical cure in 90 patients (60 per cent).

The clinical cure rate for those patients with axillary node metastases was 21 per cent and is a lower rate, by as much as 10 to 18 per cent, when compared to the results in all age groups. Without node involvement, the clinical cure rate of 60 per cent seemed lower than one might expect. These low figures might be explained by the fact that only cases of histologically confirmed axillary node involvement were accepted and that survivors in whom the node status was unknown were excluded rather than included as being "uninvolved." The over-all survival rate in this group (136 patients of 367) was 37 per cent.

The location of the breast tumor in 398 patients (99.4 per cent) of the operable group was as follows: upper outer quadrant in 200 patients (50.0 per cent), lower outer quadrant 35 (9.0 per cent), upper inner quadrant 73 (18.0 per cent), lower inner quadrant 20 (5.0 per cent), vertical midline 39 (10.0 per cent), horizontal midline (medial) 2 (0.5 per cent), horizontal midline (lateral) 4 (0.9 per cent), central (subareolar) 16 (4.0 per cent), locally advanced 9 (2.0 per cent). The minimum clinical cure rates are given in Table VIII. Cancers occurring in the lateral half of the breast yielded a clinical cure rate of 35.5 per cent as compared to 34.7 per cent when the tumor was in the medial half of the breast, excluding vertical midline and subareolar lesions. If one included midline and subareolar tumors with those located in the inner quadrants, the clinical cure rate was 38.6 per cent by the usual methods of surgical therapy.

TABLE VIII.—LOCATION OF TUMOR AND CLINICAL CURE RATE IN 398 PATIENTS

Location	*No. patients*	*5 year clinical cure*	
		No.	*Per cent*
Upper inner quadrant	73	22	30.1
Lower inner quadrant	20	9	45.0
Vertical midline	39	17	43.0
Horizontal midline (medial)	2	2	100.0
Central (subareolar)	16	8	50.0
	150	58	38.6
Upper outer quadrant	200	75	37.5
Lower outer quadrant	35	10	28.5
Horizontal midline (lateral)	4	0	0.0
	239	85	35.5
Locally advanced	9	2	22.2

TABLE IX.—AGE GROUP AND CLINICAL CURE, 420 OPERABLE PATIENTS

	Age group		
	19–25	*26–30*	*31–35*
No. patients	19	105	296
Failures	15	59	177
5 year survivals	5	46	119
Clinical cure, per cent	21.0	43.8	40.2

There were 420 patients in the operable group for evaluation; 28 who died of other diseases or were lost to follow-up were excluded, but those who refused treatment were included. Table IX gives the results as to clinical cure for the following age groups: 19 to 25, 26 to 30, and 31 to 35. These data suggest that one cannot predict the results of treatment for any specific age below 35 years on the basis of age alone. There was an apparent reduction in the rate to 21 per cent for the 19 to 25 age group, but this group comprised 19 patients, a small number which may not be statistically significant.

In this series, outer quadrant lesions showed a higher frequency of metastases to the homolateral axillary nodes than those lesions arising in the inner quadrants (Table X). When axillary nodes were involved (Table XI), the 5 year clinical cure rate was essentially the same (19 vs. 21.9 per cent) whether the tumor was located in the inner or the outer half of the breast. When axillary nodes were not involved, cancers located in the outer half of the breast had an 8 per cent better clinical cure rate (64.8 per cent)

TABLE X.—LOCATION OF CANCER AND INCIDENCE OF INVOLVED AXILLARY NODES, 398 PATIENTS

Location	*Nodes (+)*	*Per cent**	*Nodes (−)*	*Nodes (?)*	*Total*
Upper inner quadrant	30	44.1	38	5	73
Lower inner quadrant	5	27.7	13	2	20
Upper outer quadrant	124	67.0	61	15	200
Lower outer quadrant	20	62.5	12	3	35
Vertical midline	18	51.4	17	4	39
Horizontal midline (medial)	1	50.0	1	0	2
Horizontal midline (lateral)	2	66.6	1	1	4
Central	9	60.0	6	1	16
Locally advanced	8	88.8	1	0	9
Total	217	59.1	150	31	398

*Percentages exclude those patients whose axillary node status was unknown.

compared with the clinical cure rate for inner half, midline, and central lesions combined (56 per cent). It was noted that the 5 year clinical cure rate for upper inner quadrant lesions without axillary node involvement (47 per cent) was considerably lower than the rate of 69 per cent for upper outer quadrant lesions which had not metastasized to the axillary lymph nodes. This ratio was reversed for the lower quadrants without axillary node involvement, i.e., lower inner quadrant lesions yielded better results (61 per cent) than lower outer quadrant lesions (50 per cent).

The histologic type and clinical cure rates were evaluated in the operable group of 407 patients (Table XII). Although the number of patients was too small in groups other than infiltrating duct carcinoma, the clinical cure rates would suggest a more favorable prognosis for the less common types of breast cancer, i.e., medullary, comedo, and colloid. The incidence of axillary node metastases was likewise lower in the less frequent histologic types (except for 1 case of gelatinous carcinoma). A comparison of the graded cases of infiltrating duct carcinoma showed a 78 per cent incidence of axillary node metastases in grade 3 and a 5 year clinical cure rate of 27 per cent; whereas grade 2 showed a 60 per cent incidence of axillary node metastases and a 5 year clinical cure rate of 36 per cent.

TABLE XI.—CANCER LOCATION AND NODAL INVOLVEMENT, 358 PATIENTS

Location	*No. patients*	*5 year clinical cure*	
		No.	*Per cent*
Inner half, midline, and central			
Positive nodes	63	12	19.0
Negative nodes	75	42	56.0
Outer half			
Positive nodes	146	32	21.9
Negative nodes	74	48	64.8
Total	358	134	

The 9 locally advanced patients have been excluded.

The level of node involvement was evaluated in 196 patients. Level 1 included those nodes lateral and inferior to the pectoralis minor muscle; level 2, nodes behind the pectoralis minor; and level 3, nodes medial and superior to the muscle. Skipping of a level, e.g., involvement of only level 2 without involvement of level 1, occurred in 22 per cent of the patients. The highest level involved yielded the following data: level 1, 44 patients, 34 per cent 5 year clinical cure; level 2, 58 patients, 27.6 per cent 5 year clinical cure; level 3, 94 patients, 16 per cent 5 year clinical cure. It was apparent that the higher the level of involvement, the poorer was the prognosis. If, as Berg suggests, metastases to the axillary nodes progress in a stepwise fashion from level 1 to level 3, prompt surgical therapy must be considered extremely important in the management of the patient with breast cancer. From biopsy of a node at level 3 which contains cancer one cannot declare a patient hopelessly inoperable.

INFLUENCE OF ASSOCIATED PREGNANCY

In evaluating the influence of pregnancy on breast cancer it seemed logical to differentiate between those patients who had breast cancer simultaneous with pregnancy or immediately postpartum, and those who became pregnant subsequent to therapy. The patients who became pregnant subsequently represent a naturally selected group. Others with a more aggressive clinical setting

TABLE XII.—HISTOLOGIC TYPE AND CLINICAL CURE IN 407 PATIENTS

Diagnosis	*No. patients*	*Positive nodes, per cent*	*5 year cure, per cent*	*Negative nodes, per cent*	*5 year cure, per cent*	*Over-all 5 yr. clinical cure, per cent*
Infiltrating duct ca.	356					
Ungraded, 60		51	30	49	69	49
Grade 1, 1				100	100	100
Grade 2, 149		60	26	40	51	36
Grade 3, 144		78	19	22	57	27
Grade 4, 2		50	0	50	100	50
Medullary carcinoma	21	28	60	72	77	72
Comedo carcinoma	7			100	100	100
Infiltrating, 4				100	100	100
Noninfiltrating, 3				100	100	100
Papillary carcinoma	8			100	88	88
Infiltrating, 3				100	75	75
Noninfiltrating, 5				100	100	100
Colloid carcinoma	5			100	80	80
Paget's disease with:	4	25	100	75	66	75
Infilt. duct ca., 2		50	100	50	100	100
Noninfilt. duct ca., 1				100	0	0
Noninfilt. duct comedocarcinoma, 1				100	100	100
Lobular carcinoma	3	?	—	?	—	100
Infiltrating, 1				100	100	100
In situ, 2		?	—	?	—	100
Gelatinous carcinoma	1	100	0			0
Spindle cell carcinoma	1			100	0	0
Squamous carcinoma	1			100 died of pulmonary tbc. 2 years		
Total	407					

succumbed to the cancer shortly after treatment. This natural selection would lead one to expect better results in the subsequently pregnant group. The group with simultaneous mammary cancer consisted of those patients in whom a diagnosis of breast carcinoma was made during the gestational phase or within 9 months from the date of delivery, irrespective of their nursing history. There was a total of 108 patients in whom pregnancy was associated with breast cancer. Of these, 78 had simultaneous pregnancy and 30 were pregnant subsequently. In the former group, the 5 year clinical cure rate (total experience) was 17.9 per cent, as compared to 30.7 per cent for the entire series. In the subsequently pregnant group, the clinical cure rate was 56.7 per cent. The 5 year clinical cure rate of the total group of 108 patients was 28.7 per cent, a figure which does not indicate the striking difference between the respective groups.

On the basis of the data in Table XIII concerning the simultaneous group (78 patients), pregnancy per se did not seem to be a true criterion of inoperability. The poor result in total experience might be attributed to a higher rate of inoperability at the time of admission. Nevertheless, the clinical cure rate was continued at a lower level in the patients who were operable. In this series, breast cancer appeared to be more aggressive when pregnancy was associated simultaneously. The 27 inoperable patients all died in less than 5 years and most were lost within 1 to 2 years after admission.

In the simultaneously pregnant group, 77 per cent of the operable patients had histologic evidence of axillary node metastases, again indicating a more locally advanced situation than that encountered in all patients (59.1 per cent with axillary node metastases), yet the clinical cure rate (20 per cent) with involved nodes was not different from all patients in the same classification (21 per cent). It should be noted that no patient with involved nodes at all levels who was simultaneously pregnant survived for 5 years. Those without nodal involvement showed a 50 per cent 5 year clinical cure

TABLE XIII.—CLINICAL CURE RATE IN PREGNANCY, OPERABLE PATIENTS ONLY

	No. patients	*Minimum 5 yr. clinical cure, per cent*
Simultaneously pregnant	51	27.6
Nonsimultaneously pregnant	397	39.0
Entire series (pregnant or not)	448	37.7

TABLE XIV.—MANAGEMENT OF SUBSEQUENT PREGNANCY UNINVOLVED AXILLARY NODES, 19 PATIENTS

	No. patients	Died or living with cancer	5 year clinical cure	
			No.	Per cent
Therapeutic abortion	11	2	9	81.8
Carried to term	8	4	4	50.0
Total	19	6	13	68.4

TABLE XV.—MANAGEMENT OF SUBSEQUENT PREGNANCY INVOLVED AXILLARY NODES, 10 PATIENTS

	No. patients	Died or living with cancer	5 year clinical cure	
			No.	Per cent
Therapeutic abortion	4	2	2	50.0
Carried to term	6	4	2	33.3
Total	10	6	4	40.0

TABLE XVI.—DELAY, INCIDENCE OF AXILLARY NODE METASTASES, AND CLINICAL CURE RATES IN 341 PATIENTS

Delay, months	No. patients	Per cent + nodes	5 year clinical cure
<1	136	61	40.4
2	54	61	42.6
3 to 4	56	51	42.8
5 to 6	30	53	46.6
7 to 9	27	55	37.0
10 to 12	23	69	30.4
>12	15	73	33.3

TABLE XVII.—SIZE OF TUMOR AND INCIDENCE OF METASTATIC AXILLARY NODES IN 224 PATIENTS WITH INFILTRATING DUCT CARCINOMA

	Patients		Positive nodes,
Tumor size, cm.	No.	Per cent	per cent
1 or less	23	10.2	39.1
1.1 to 2.0	65	29.0	53.8
2.1 to 3.0	62	27.6	67.7
3.1 to 4.0	23	10.2	91.3
4.1 to 5.0	30	13.3	86.6
5.1 to 6.0	11	4.9	100.0
6.1 to 7.0	5	2.2	80.0
7.1 to 8.0	–	–	–
8.1 to 9.0	3	1.3	100.0
>9	2	0.8	100.0
Total	224		Average 68.3

2 cm. or less, positive nodes, 50.0 per cent.
>2 cm., positive nodes, 80.1 per cent.

3 cm. or less, positive nodes, 57.3 per cent.
>3 cm., positive nodes, 90.5 per cent.

rate compared to 60 per cent for all patients in the same classification.

In 36 patients a breast mass was discovered during one of the trimesters of pregnancy. The remaining 42 patients discovered a breast mass following delivery or immediately after a spontaneous miscarriage. In 27 patients, the decision regarding the management of the pregnancy had been made by the responsible obstetrician or surgeon, and the patient was then referred to Memorial Center. Of the 36 patients in the gestational phase, there were 16 in the first trimester, 14 in the second trimester, and 6 in the third trimester. In the first trimester of pregnancy, the only 2 survivors were treated by therapeutic abortion and radical mastectomy. Five other patients similarly treated did not survive. In the second trimester the total group was likewise small, 3 survivors among 14 patients. In none of the patients was the pregnancy terminated. Two of the 3 survivors were without involvement of axillary nodes. In the third trimester of pregnancy no attempt was made to influence the pregnancy and 3 of 6 patients were free of cancer at 5 years.

We have been unable to draw any definite conclusions concerning the management of pregnancy for the woman with concurrent breast cancer on the basis of the data first given. At present, it can only be suggested that the responsible surgeon consider the clinical setting of each patient, the religious attitudes, and the individual problems before deciding on a plausible clinical approach.

Thirty patients became pregnant at some time after treatment for breast cancer. The 5 year clinical cure rate in this group was 56.6 per cent. The fact that 63.3 per cent of these patients did not have involved axillary nodes at the time of initial surgery would lead one to anticipate a more favorable prognosis. Table XIV records the management of the pregnancy and the results in the group with uninvolved axillary nodes. It would appear that when therapeutic abortion was employed a more favorable prognosis was obtained. But in some of these patients there was reasonable doubt that pregnancy itself or the termination of the pregnancy had any influence on the course of the disease. Table XV records similar data for those patients with involved axillary lymph nodes. Again the results seem more favorable in those patients whose pregnancies were terminated.

SIGNIFICANCE OF DELAY

The delay interval between the onset of symptoms and the first visit to Memorial

Center was available for 393 operable patients. The median delay was 2 months; the range extended from 1 day to over 1 year. The relationship between delay, the incidence of metastatic axillary nodes, and the clinical cure rates are reported in Table XVI for 341 operable patients when all three factors were known. There was some variation in the findings within the individual monthly brackets. However, if the groups are combined into 6 months' delay and delay longer than 6 months, the results were quite different from those reported by MacDonald.

In our series, the 116 patients who were seen within 6 months showed a 58.3 per cent incidence of metastatic axillary nodes and a clinical cure rate of 42 per cent; for 65 patients seen after a period of 6 months the incidence of metastatic axillary nodes was 64.6 per cent and the 5 year clinical cure rate was only 33.8 per cent. The median delay in those simultaneously pregnant was 4 months, twice as long as the nonpregnant women. This may partially account for the higher incidence of metastatic axillary nodes and a lower clinical cure rate in the former group.

SIZE OF THE TUMOR

Accurate information in the study of tumor size was found in the primary operable group. In 254 patients the dimensions were recorded by the pathologist and the follow-up was adequate. Diagnoses other than infiltrating duct carcinoma were noted in 26 instances. Infiltrating duct carcinoma was found in 228 patients, and of these, 4 were excluded because of unknown axillary lymph node status. Table XVII records the size of the tumor and the incidence of axillary lymph node involvement. The incidence of axillary lymph node metastasis increased with the tumor size. Considering only the size of the tumor, it becomes apparent from Table XVIII that the 5 year clinical cure rate definitely diminished as the tumor size increased. From the data in Tables XIX and XX it would appear that tumor size alone was of significant prognostic import. A comparison of patients with uninvolved axillary nodes and varying sized tumors showed that the smaller the tumor the better the prognosis. In patients with involved axillary nodes this relationship also held true, except for tumors smaller than 1 centimeter in diameter. Since there were only 9 patients in the latter group, the sample may be too small to warrant drawing any conclusions.

If the 26 patients whose tumors were not diagnosed as infiltrating duct carcinoma were included in the total evaluation of

TABLE XVIII.—TUMOR SIZE ALONE RELATED TO CLINICAL CURE RATE IN 224 PATIENTS WITH INFILTRATING DUCT CARCINOMA

Tumor size, cm.	*No. patients*	*Per cent 5 year clinical cure*
1 or less	23	65.2
1.1 to 2.0	65	44.6
2.1 to 3.0	62	32.3
3.1 to 4.0	23	17.3
4.1 to 5.0	30	13.3
5.1 to 6.0	11	18.1
6.1 to 7.0	5	40.0
7.1 to 8.0	–	–
8.1 to 9.0	3	0.0
>9	2	0.0

1 cm. or less, 65.2 per cent, 5 year clinical cure
>1 cm., 30.3 per cent, 5 year clinical cure
2 cm. or less, 50.0 per cent, 5 year clinical cure
>2 cm., 23.5 per cent, 5 year clinical cure
3 cm. or less, 42.6 per cent, 5 year clinical cure
>3 cm., 16.2 per cent, 5 year clinical cure

TABLE XIX.—CLINICAL CURE RELATED TO SIZE OF TUMOR AND METASTATIC AXILLARY NODES

	Positive nodes		*Negative nodes*	
Size of tumor, cm.	*No. patients*	*Per cent 5 yr. clinical cure*	*No. patients*	*Per cent 5 yr. clinical cure*
1 or less	9	11.1	14	100.0
1.1 to 2.0	35	34.2	30	56.6
2.1 to 3.0	42	21.4	20	55.0
3.1 to 4.0	21	14.2	2	50.0
4.1 to 5.0	26	11.5	4	25.0
5.1 to 6.0	11	18.1	—	—
6.1 to 7.0	4	25.0	1	100.0
7.1 to 8.0	—	—	—	—
8.1 to 9.0	3	0.0	—	—
>9	2	0.0	—	—
Total	153	Aver. 20.2	71	Aver. 63.3

TABLE XX.—CLINICAL CURE RELATED TO SIZE OF TUMOR AND METASTATIC AXILLARY NODES

	Positive nodes		*Negative nodes*	
Size of tumor, cm.	*No. patients*	*Per cent 5 yr. clinical cure*	*No. patients*	*Per cent 5 yr. clinical cure*
1 or less	9	11.1	14	100.0
>1	144	20.8	57	54.3
2 or less	44	29.5	44	70.4
>2	109	16.5	27	51.8
3 or less	86	25.5	64	65.6
>3	67	13.4	7	42.8

TABLE XXI.—POSTOPERATIVE X-RAY THERAPY AND CLINICAL CURE RATES, 368 PATIENTS

	No. patients	*Died*	*5 yr. clinical cure*	
			No.	*Per cent*
Positive axillary nodes	219	167	52	23.7
X-ray therapy.....	175	135	40	22.8
No x-ray therapy..	44	32	12	27.2
Negative axillary nodes	149	57	92	61.7
X-ray therapy.....	44	20	24	54.5
No x-ray therapy..	105	37	68	64.7

tumor size or lymph node status, the conclusions would have been weighted by the varying histologic types. Of 12 patients with medullary carcinoma, the tumor was greater than 4 centimeters in 50 per cent (compared to 22 per cent for infiltrating duct carcinoma) and the axillary lymph nodes were involved in 33 per cent (compared to 68.3 per cent for infiltrating duct carcinoma). An erroneous conclusion might have been made from these data that tumor size had little influence on the incidence of axillary lymph node involvement or on the prognosis. The 5 year clinical cure for the 12 patients with medullary carcinoma was 75 per cent. Similar findings were noted in other pathologic groups.

INFLUENCE OF POSTOPERATIVE X-RAY THERAPY

There were 368 operable patients available for evaluation of the influence of postoperative x-ray therapy on clinical cure rates. There have been many improvements in the technique of high voltage x-ray therapy since 1939. Nevertheless, the type of therapy given in the years under study was considered to be adequate at the time, just as the x-ray therapy today is thought to be the best available. One could only use the data at hand, allowing for variations in technique, and present the results as they appeared in the cases under study (Table XXI). For patients with axillary node metastases, x-ray therapy did not improve the clinical cure rate. When no x-ray therapy was given, the clinical cure rate was slightly higher. Patients without axillary node metastases who had not received x-ray therapy showed a higher clinical cure rate than those who were treated.

Of 448 patients in the operable group there were 257 instances in which the cancer definitely was not controlled. There were 249 patients considered dead of disease and 8 living with disease after 5 years. The latter group varied in duration from 6 to 12 years. The median duration of life was 2 years and 2 months. Of the patients who died, almost one-fourth succumbed within the first year. By the end of the second year almost one-half had died. More than two-thirds had died by the end of the third year. Although there was a continuing loss through the ninth year, when the patient had passed the fifth year the chances were strongly in her favor that she would continue to do well.

There were 169 patients who were free of cancer for 5 years or longer. Of these, 160 patients (95 per cent) had radical mastectomy. Of the remaining 9 patients, 4 had simple mastectomy and 5 were treated by local excision only since these had cancers which were noninvasive.

There was no postoperative mortality in 399 patients treated by radical mastectomy nor in the patients treated by local excision or simple mastectomy.

EFFECT OF CASTRATION

In the operable group, 49 patients had castration following treatment for breast cancer at a time when there was no clinical evidence of recurrence. The vast majority, during the years under study, received pelvic radiation to suppress ovarian function. In Table XXII, a comparison of survivors in the castrated and noncastrated groups has been made. The results indicated that there was little difference in clinical cure rates when the axillary nodes were uninvolved and prophylactic castration was done (60 vs. 62.9 per cent). When the axillary nodes were involved, the 5 year clinical cure rate was 8.3 per cent higher (22.4 vs. 30.7 per cent) in those patients who were castrated prophylactically.

The results have also indicated that in those patients in the castrated group with positive axillary nodes who failed to respond

there was a shorter duration of life by 7 months than in those who were not castrated. This was difficult to reconcile with the fact that castrated patients who had involved axillary nodes showed a better 5 year clinical cure rate. But the lack of correlation was due probably to the small numbers of patients in the castrated group. In a recent report on the evaluation of prophylactic castration a similar observation on a much larger group of patients was made by Treves (11).

In the entire series of 549 patients, 73 were castrated for recurrent local or metastatic disease. The duration of life following therapeutic castration varied from 1 month to a maximum of 2 years and 10 months. The median length of survival following therapeutic castration was 9 months. This result was in accord with the results obtained in a larger group of patients who had therapeutic castration (12).

BILATERAL BREAST CANCER

There were 23 patients with bilateral breast cancer (2 occurring simultaneously and 21 nonsimultaneously) among the 418 patients in the operable group. The designation of bilaterality was based on Farrow's criteria. The incidence of nonsimultaneous bilateral breast cancer was 5 per cent. This might indicate that a prophylactic simple mastectomy performed on the remaining breast would have been unnecessary in 397 patients or 95 per cent of the series.

Should prophylactic simple mastectomy be done in young women with a pertinent family history of breast cancer? Of the 21 patients with nonsimultaneous bilateral breast cancer, the family history was unknown in 3, negative in 15, and positive for breast cancer in 4. In the remaining 418 patients, there was a family history of breast cancer in 41; in 4 of these bilateral breast cancer developed, an incidence of 9.7 per cent. Therefore, if a family history of breast cancer was used as an indication for prophylactic simple mastectomy, it would have been unnecessary in 37 of the 41 possible candidates, or in 90.3 per cent.

TABLE XXII.—PROPHYLACTIC CASTRATION VS. NO CASTRATION

	No. patients	*5 year clinical cure*		*Died*	
		No.	*Per cent*	*No.*	*Per cent*
Castration					
Positive axillary nodes.	39	12	30.7	27	69.3
Negative axillary nodes	10	6	60.0	4	40.0
	49	18		31	
No castration					
Positive axillary nodes.	178	40	22.4	138	77.6
Negative axillary nodes	135	85	62.9	50	37.1
Total.....	313	125		188	

SUMMARY AND CONCLUSIONS

An analysis has been made of 549 patients with histologically confirmed breast cancer. All were 35 years of age or younger. The following conclusions are based on a study of patients seen at Memorial Center from 1937 through 1949. More than three-fourths of the patients reported no familial history of cancer of any type. When cancer was present in the family, the breast was involved in 35 per cent; one-half reporting breast cancer in the mother and almost one-fourth in a sister. Eighty-two per cent of the patients were married and 66 per cent had been pregnant at least once. The incidence of surgical gynecologic disorders appeared to be relatively high for this young age group. In 92 per cent, the patient discovered a breast mass without medical assistance. In only 1 per cent was the tumor discovered during routine physical examination. Nipple discharge was present in 5.5 per cent, bloody discharge occurring twice more frequently than serous. Bloody discharge more often indicated an infiltrating duct carcinoma with no papillary component.

Infiltrating duct carcinoma accounted for 86.6 per cent of the pathologic diagnoses, while other histologic types were in the minority.

The minimum 5 year clinical cure rate, based on total experience, was 30.7 per cent. When selection was made in terms of operability, the 5 year clinical cure rate was 37.7 per cent. Further selection, i.e., exclusion of patients who died of other causes, were lost to follow-up without evidence of recurrent cancer, or refused treatment, yielded a

maximum rate of 40.6 per cent. These data and a review of the literature indicate that breast cancer in the young woman offers a prognosis equal to that of older women.

When axillary node involvement was present, the clinical cure rate was lower than that found in older women, suggesting that the disease may be more lethal when regional metastases have occurred in the young patient.

In this series, the specific location of the tumor within the breast had little or no influence on the rate of clinical cure.

One cannot predict the results of treatment for any specific age below 35 years on the basis of age alone.

Outer quadrant lesions showed a higher frequency of axillary node metastases than those arising in the inner quadrants, yet the 5 year clinical cure rate was essentially the same whether the tumor was located in the inner or outer half of the breast. When axillary nodes were not involved, cancers located in the outer half of the breast had an 8 per cent better clinical cure rate, compared with the rate for inner half, midline, and central lesions combined.

The prognosis was better for those patients with the less common type of breast cancer, e.g., medullary, comedo, and colloid carcinoma, than for infiltrating duct carcinoma. The incidence of axillary node metastasis was likewise lower. Infiltrating duct carcinoma grade 2 showed a lower incidence of axillary node metastases and a higher clinical cure rate than grade 3. The higher the level of axillary node involvement, the poorer was the prognosis. Involvement of level 3, however, should not be used as a criterion of inoperability, since 16 per cent of these patients were free of recurrent cancer 5 years or more after radical mastectomy.

Although pregnancy occurring simultaneously with breast cancer had an extremely poor prognosis, the pregnancy should not be utilized as a criterion of inoperability. Pregnancy occurring at some time subsequent to surgical therapy for breast cancer appeared to have little influence on prognosis. Definite conclusions concerning the management of pregnancy for women with concurrent breast cancer could not be formulated. Likewise, no recommendations can be made regarding management of pregnancy for the woman who has been treated previously for breast cancer.

Patients who delayed longer than 6 months before surgical treatment showed a higher incidence of axillary node metastases and a lower clinical cure rate than patients who sought medical care earlier.

Postoperative x-ray therapy, regardless of axillary node involvement, had no influence on the clinical cure rates.

Patients considered clinical failures had a median duration of life slightly over 2 years. More than two-thirds had died by the end of the third year.

There was no postoperative mortality in 399 patients treated by radical mastectomy.

When the axillary nodes were uninvolved, prophylactic castration did not affect the clinical cure rates. When axillary nodes were involved, the 5 year clinical cure rate was 8.3 per cent higher in those patients who were castrated prophylactically.

No comparison could be made between the effectiveness of surgical castration and pelvic radiation. The median duration of survival following therapeutic castration for metastatic breast cancer was 9 months.

Prophylactic simple mastectomy is not to be recommended even in the presence of a significant familial history of breast cancer.

The incidence of axillary node metastasis increased proportionately with the size of the tumor. The 5 year clinical cure rate diminished as the size of the tumor increased. Tumor size alone was of significant prognostic import, whether the axillary nodes were involved or free of metastases.

From these studies we would suggest that certain stringent criteria of operability, which in the past have been given fairly wide attention, be modified. Even young women with axillary node metastases at the highest level have a 16 per cent chance for

5 year clinical cure. Early diagnosis and prompt radical surgery offer the best chance for survival. When the primary lesion is small and still localized to the breast the maximum opportunity for 5 year clinical cure exists. Tumors occurring in the breast during pregnancy should be diagnosed and treated immediately. The previous impressions of poor prognosis for breast cancer in the young woman who is not concurrently pregnant must be supplanted by a more hopeful outlook.

REFERENCES

1. ADAIR, F. E. Surgical problems involved in breast cancer (Moynihan lecture). Ann. R. Coll. Surgeons England, 1949, 4: 360–380.
2. BERG, J. W. The significance of axillary node levels in the study of breast carcinoma. Cancer, 1955, 8: 776–778.
3. DE CHOLNOKY, T. Mammary cancer in youth. Surg. Gyn. Obst., 1943, 77: 55–60.
4. EWING, J. Neoplastic Diseases; a Treatise on Tumors. 4th ed. Philadelphia: W. B. Saunders Co., 1940.
5. FARROW, J. H. Bilateral mammary cancer. Cancer, 1956, 9: 1182–1188.
6. GROSS, S. W. A Practical Treatise on Tumors of the Mammary Gland; Embracing Their Histology, Pathology, Diagnosis, and Treatment. P. 146. New York: D. Appleton & Co., 1880.
7. LEE, B. J. Carcinoma of breast in young. Arch. Surg., 1931, 23: 85–110.
8. MACDONALD, I., and WILCOX, N. E. Prognosis of mammary carcinoma in young women. Cancer, 1956, 9: 281–289.
9. NATHANSON, I. T., and WELCH, C. E. Life expectancy and incidence of malignant disease—I, carcinoma of breast. Am. J. Cancer, 1936, 28: 40–53.
10. TAYLOR, G. W. Carcinoma of breast in young women. N. England J. M., 1936, 215: 1276–1278.
11. TREVES, N. Evaluation of prophylactic castration in treatment of mammary carcinoma; analysis of 152 patients. Cancer, 1957, 10: 393–407.
12. TREVES, N., and FINKBEINER, J. Evaluation of therapeutic surgical castration in treatment of metastatic, recurrent, and primary inoperable mammary carcinoma in women; analysis of 191 patients. Cancer, in press.
13. WESTBERG, S. V. Prognosis of breast cancer for pregnant and nursing women; clinical-statistical study. Acta. obst. gyn. scand., 1946, 25 (Suppl. 4): 1–237.

PULMONARY LYMPHATIC DRAINAGE IN THE DOG

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PERHAPS THE MOST WIDELY QUOTED of all studies having to do with the lymphatics of the pulmonary system are those of Rouvière (4–7). His reports were based on findings in 200 newborns, fetuses, and infants. Probably the most controversial portion of his results is the lymphatic drainage route of the left lower lobe. He stated that he made 25 injections of the lower lobe and 10 injections of the hilar node near the left inferior pulmonary vein. From these 35 preparations he concluded that most of the left lower lobe (the inferior portion) is drained to the left subcarinal node whence the lymph crosses to the right subcarinal node and then drains up the right paratracheal lymphatic chain. This pathway of the left lower lobe lymphatic drainage has been widely quoted. Rouvière presented 2 examples of injected specimens which purported to show the pathways by which lymph could drain from each lower lobe via the inferior pulmonary ligament lymphatic channel to supradiaphragmatic and infradiaphragmatic nodes.

On the basis of Rouvière's findings, Connar has recently stated that, in clinical cases, if scalene node biopsy is to be done for a left lower lobe lesion, it should be performed on the right. This concept of left lower lobe lymphatic drainage is at variance with Most (2, 3) who stated in 1908 that the lobes of the lung do not have distinct lymphatic territories, but that lymphatics from the mid and inferior portions of the lungs go to the subcarinal nodes. The lymph from middle and superior portions go to the paratracheal nodes.

From the Departments of Surgery, Chicago State Tuberculosis Sanitarium and The University of Illinois College of Medicine, Chicago.

In 1942, Warren and Drinker, working with dogs, cannulated the right tracheal lymph duct as well as the thoracic duct. Three cubic centimeters of T-1824 (Evans blue) in saline were then instilled into a lower lobe bronchus. The dye always appeared on the right first, no matter where it was placed. Their conclusions included the statement that "the drainage of lymph from both lungs is in the main via the right lymphatic duct, comparatively little being delivered to the circulation by the thoracic duct."

METHODS

The lymph drainage of each lobe of lung in the dog was investigated by a visual method. A measured amount of pigment was deposited in the parenchyma of the lobe in question. Subsequent examination of all lymph nodes of the neck and thorax revealed some of them to be colored by the pigment.

The coloring matter used was a 10 per cent suspension in saline of alphacolor dry pigment tempera.[1]

Adult mongrel dogs were anesthetized with nembutal. A 7-40 Jackson bronchoscope was passed into the trachea. By means of a Moersch needle, 2 cubic centimeters of the pigment suspension were injected into the peribronchial area of a segmental bronchus of the lobe being investigated. By using different colors, the lymph node spread from more than one lobe could be demonstrated in the same dog. Occasionally part of the dye was accidentally injected into

[1]The pigment particles are both organic and inorganic with an average particle size of from 5 to 10 microns. The binder is a carbohydrate derivative which is also nontoxic. There is less than ½ per cent of sodium orthophenyl phenol used as preservative.

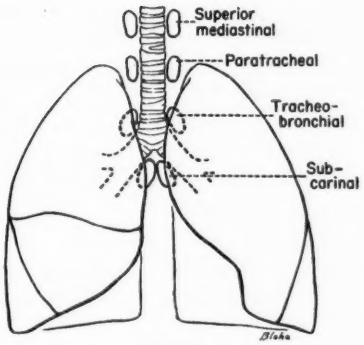

FIG. 1.

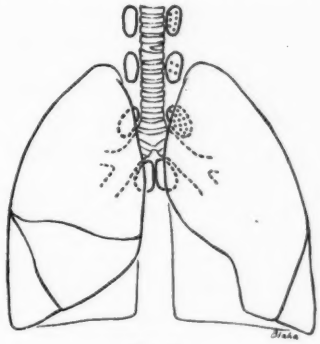

FIG. 2.

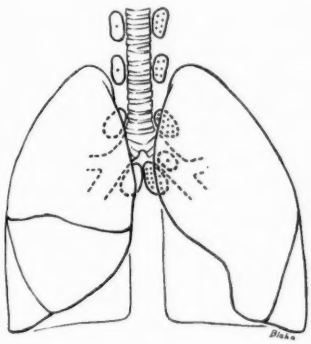

FIG. 3.

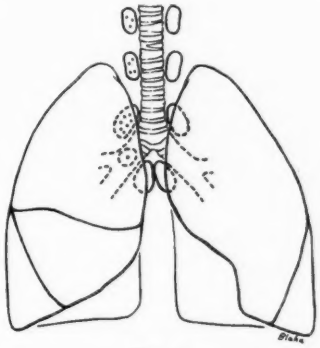

FIG. 4.

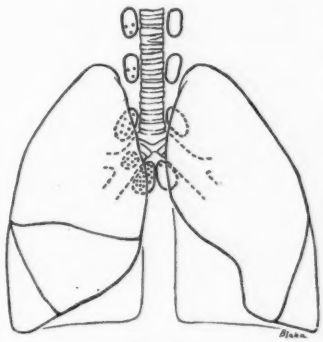

FIG. 5.

FIG. 1. Nomenclature for tracheobronchial lymph nodes.
FIG. 2. Left upper lobe injected in 13 cases.
FIG. 3. Left lower lobe injected in 14 cases.
FIG. 4. Right upper lobe injected in 12 cases.
FIG. 5. Right lower lobe injected in 17 cases.

the pleural space, in which case the lymph node spread of that particular color was disregarded and not included in the series. Four to 6 days following deposition of the colored pigment, the animals were exsanguinated and autopsied, and the entire thoracic content was removed as an en bloc specimen, including the superior mediastinal and the low cervical structures. This specimen was fixed in 10 per cent formalin and then dissected. Positive lymph nodes were easily identified and plotted for each lobe by matching the color of the deposit in the different lobes of lung with the color of deposit in the lymph nodes. In many instances a node was multicolored, signifying that it received lymph drainage from the different lobes of lung containing each color.

The anatomic arrangement of the lymph nodes of the dog is reasonably constant. The most distal node is the subcarinal node, which is usually paired. The tracheobronchial nodes are at the tracheobronchial angle of each upper lobe, in the "aortic window" on the left and in the "azygos window" on the right. There are paratracheal nodes between the aortic arch and thoracic inlet on the left and between the azygos vein and the thoracic inlet on the right. The lymph nodes above the thoracic inlet are called superior mediastinal nodes in this article. The superior mediastinal nodes are nested along the subclavian ves-

sels in the deep cervical and upper mediastinal tissues. In addition to these nodes which are constant, one frequently finds a right retrobronchial node behind the intermedius bronchus and occasionally there is a left retrobronchial node behind the left main stem bronchus.

The nomenclature for identifying the different tracheobronchial lymph nodes will thus be: right and left subcarinal; right and left tracheobronchial; right and left retrobronchial; right and left paratracheal; and right and left superior mediastinal (Fig. 1). The bronchopulmonary nodes found around the segmental bronchi in the human were not found in the dog.

RESULTS

Thirteen left upper lobes were injected. The left tracheobronchial node always contained pigment. The left paratracheal node was positive in 4 of these, and the left superior mediastinal node was positive in 7. In no case were the subcarinal nodes involved (Fig. 2).

Fourteen left lower lobes were injected. The left subcarinal node was positive in 13 of these. The left tracheobronchial node was positive on 10 occasions, the left paratracheal in 6, and the left superior mediastinal node was involved 7 times. The right paratracheal and superior mediastinal nodes were positive in 1 animal (Fig. 3). In 1 animal there was no occurence of lymph node spread.

Twelve right upper lobes were injected. Lymph node spread was present in only 7, in which the right tracheobronchial nodes were positive. The right paratracheal nodes were positive in 4 animals and the right superior mediastinal nodes were positive in 3 (Fig. 4).

Seventeen dogs were given right lower lobe injections. The right subcarinal node was always positive; the left subcarinal node was positive once. The right retrobronchial node was present and involved 6 times and the right tracheobronchial node 7 times. The right paratracheal and right superior mediastinal nodes were each positive in 3 dogs (Fig. 5).

Three dogs had injection of the right middle lobe. Twice the right subcarinal node and right retrobronchial node were involved. The right tracheobronchial and right superior mediastinal nodes were positive once each.

SUMMARY

1. The pattern of lymphatic drainage from the lungs of dogs is basically ipsilateral in distribution. (a) Each upper lobe drains to a corresponding paratracheal and superior mediastinal chain. (b) Each lower lobe drains to the corresponding subcarinal node and thence to the ipsilateral paratracheal chain as a rule.

2. Crossing of lymph drainage from the lower lobe occurs from either side but is uncommon.

3. This study is at variance with the currently publicized patterns of lymphatic drainage, upon which management of clinical cases is being predicated. The fact that our work was carried out on dogs need not cause it to be deprecated in this regard since the former work was likewise largely done on dogs.

REFERENCES

1. Connar, R. G. Prescalene and deep cervical lymph node biopsy. Surg. Gyn. Obst., 1955, 101: 732.
2. Most, A. Die Topographie des Lymphgefassapparates des menschlichen Körpers und ihre beziehungen zu den Infektionswegen der Tuberkulose. Bibliotheca Medica, Abteilung C; Pathologie und Pathologische Anatomie. Heft 21. Stuttgart: E. Nägele, 1908.
3. Idem. Chirurgie der Lymphgefaesse und der Lymphdruesen; neue deutsche Chirurgie. 24. Band. Pp. 3–402. Stuttgart: F. Enke, 1917.
4. Rouvière, H. Anatomie des lymphatiques de l'homme. Paris: Libraires de l'académie de médecine, 1932.
5. Idem. Sur les connexions des lymphatiques du lobe inférieur du poumon gauche avec les ganglions paratrachéaux droits et sus-claviculares droits. Ann. anat. path., Par., 1928, 5: 743.
6. Idem. Variations dans la disposition des lymphatiques de la base des lobes inférieurs des poumons. Ann. anat. path., Par., 1928, 5: 1002.
7. Idem. Les vaisseaux lymphatiques des poumons et les ganglions viscéraux intrathoraciques. Ann. anat. path., Par., 1929, 6: 113.
8. Warren, M. F., and Drinker, C. K. The flow of lymph from the lungs of the dog. Am. J. Physiol., 1942, 136: 207.

A SLOW INJECTION METHOD OF AORTO-ARTERIOGRAPHY

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OUTLINING the aorta and the main arterial branches beyond its bifurcation by means of radiopaque materials, with roentgenographic recording of the images, has become an indispensable technique in the planned surgical treatment of these vessels, particularly in arteriosclerotic obliterative disease.

The method of aortography that we use almost always makes it possible to demonstrate the arteries of the lower extremities to a level below the knees. Furthermore, we believe that this technique offers advantages in safety to the patient and in simplicity of performance over most procedures previously described. Thus, a description of our technique appears to be justified.

TECHNIQUES OF AORTOGRAPHY AND FEMORAL ARTERIOGRAPHY

Rogoff has given an excellent historical summary of various methods of aortography and femoral arteriography. They may be briefly categorized as follows:

1. Translumbar aortography may be done by insertion of a needle into the abdominal aorta at about the level of the twelfth thoracic vertebra. Reliance is placed on rapid injection of a concentrated solution of radiopaque material, which is done either mechanically or manually. Wylie and McGuinness, and Langsam and Wilensky, varied this injection technique by placing 2 needles in the aorta about 1 inch apart and injecting opaque material from 2 syringes simultaneously through both needles in order to increase the speed of injection of the required amount of material. Multiple roentgenograms of the abdomen and extremities then are made. Many methods have been described for changing cassettes rapidly in order to obtain a roentgenographic record of the opaque material as it travels down the arteries.

2. Another major variation in the technique of examining the lower part of the abdominal aorta and the arteries of the legs is that described by de Reus and Vink in which the needle, introduced by the translumbar route, is inserted in the abdominal aorta at about the level of the third lumbar vertebra, below the origin of the renal arteries. Rapid injection again is utilized and multiple films are exposed. This technique has definite advantages in safety over the method just described.

3. Aortography may be limited to examination of the abdominal aorta and its pelvic branches, femoral arteriography being used for examination of the arteries of the legs.

4. Aortography by means of aortic catheterization via a needle in a femoral artery may be employed. Multiple exposures are used in recording the opacified arteries. The method of arterial catheterization used by Seldinger seems to simplify insertion of the catheter into the artery.

5. Astle and Wallace-Jones developed a scanographic technique including a moving x-ray tube with a beam limited by a slit diaphragm.

TECHNIQUE USED AT THE MAYO CLINIC

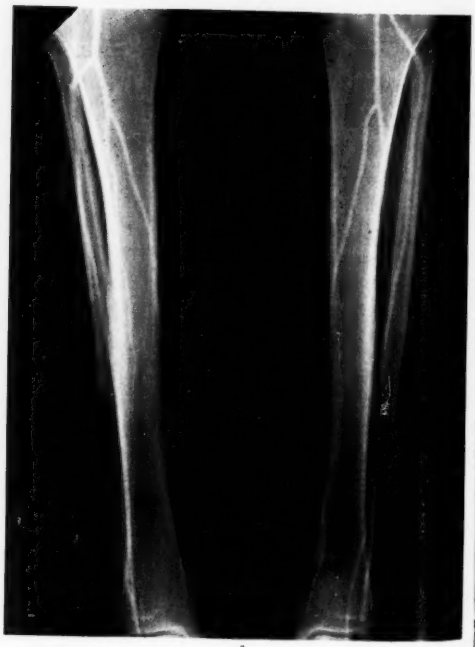
The method to be described differs in several respects from the techniques usually advocated. The implements are the same as those used for other methods of translumbar aortography. At the Mayo Clinic, aortography is performed in the Section of Roent-

From the Sections of Roentgenology and Surgery, Mayo Clinic, and the Mayo Foundation, Rochester, Minnesota.

a

c

b



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(*Legend on facing page.*)

FIG. 1. a, Roentgenogram after initial injection of a small amount of opaque material through a needle placed in the aorta at the level of the twelfth thoracic vertebra. It is obvious that the abdominal aorta is patent below the level of the renal arteries and that it will be possible to place a second needle into it above the bifurcation. b, Appearance after injection of a small amount of radiopaque material through the second needle, which was placed into the aorta well below the level of the renal arteries. c and d, Roentgenograms taken with the aid of a 36 inch cassette after slow injection of a fairly large quantity of radiopaque material into the aorta via the needle seen in "b."

genology by a roentgenologist, with the assistance of an anesthesiologist, a nurse, and a roentgenologic technician.

For the past year, our anesthesiologists have been working with lumbar epidural block, using lidocaine (xylocaine) hydrochloride and epinephrine. Sensory anesthesia at or above the eighth thoracic vertebra provides excellent conditions for both the patient and the roentgenologist.

The patient is placed prone on the table; we use a mobile cart with a flat bakelite top. On the table top are placed 2 or 3 stationary grids. The patient lies on these grids, which are placed so that they underlie the abdomen, pelvis, and lower extremities down to the middle part of the calves or the ankles. Underneath the table top is a mobile tray that can hold either a 14 by 17 inch or a 36 by 14 inch cassette.

A 6 inch, 18 gauge needle, with its stylet in place, is inserted through the skin of the left lumbar region immediately below the last rib and about 4 fingerbreadths from the midline. The needle is advanced parallel to the last rib, entering at an angle of about 60 degrees to the skin. No attempt is made to touch the vertebral body first, the needle being inserted directly toward the aorta. However, if the needle impinges on bone, it is withdrawn to just below the skin and redirected. It is advanced slowly, with the pad of the thumb on the base of the stylet, while the shaft is directed with the other hand. When the tip of the needle comes in contact with the aorta, transmitted pulsations are easily felt. The stylet is then withdrawn, and a 10 milliliter syringe filled with an isotonic solution of sodium chloride is attached to the needle by means of a 9 to 12 inch length of polyethylene tubing; this tubing connects to a one-way stopcock at the base of the syringe and it has a Luer-Lok adapter at the other end. The tubing is filled with saline before it is attached to the aortic needle. After the tubing and syringe are connected to the needle, the stopcock is placed in the open position and the needle is advanced into the aorta, a free flow of blood into the transparent tubing being the evidence of entry. If saline can be freely and easily injected, the needle is well placed. A 20 milliliter Luer-Lok syringe is filled with 12 to 15 milliliters of a 70 per cent solution of sodium acetrizoate (urokon sodium). With a 14 by 17 inch cassette under the region of the abdominal aorta and the x-ray tube centered, a rapid injection (1 to 2 seconds) is made, and a roentgenogram is taken at the end of the injection. Immediately after this injection, 10 to 20 milliliters of saline are flushed through the needle; additional small amounts are flushed through several times while the roentgenologist waits to view this first roentgenogram.

The first roentgenogram gives a good idea of the condition of the abdominal aorta and its visceral branches (Fig. 1a and 2a). Sometimes the medium has opacified the iliac arteries surprisingly well. This picture determines where the second needle should be placed in order to enter the abdominal aorta well below the main renal arteries. (If the aorta is completely obstructed well above the bifurcation and the inferior mesenteric artery, additional injections are not made and the procedure is ended; if further roentgenographic information is desired in such a case, femoral arteriography should be done.)

The second needle is now inserted into the aorta at the site determined from the first roentgenogram. If a free flow of saline is obtained into this portion of the aorta, 10 milliliters of urokon sodium are injected fairly rapidly and a 14 by 17 inch roentgenogram is made of the region at and below this needle. This injection is sufficient to give

an excellent representation of the condition of the lower abdominal aorta and of the iliac and upper femoral arteries (Fig. 1b and 2b). Note that in Figure 2b the localized constriction of the lower abdominal aorta is easily seen, whereas it is not at all well defined in Figure 2a, in which the injection was made high in the aorta. After it is seen that the second needle is well placed, the first needle may then be removed.

A 36 by 14 inch cassette is now loaded with 2 sheets of 14 by 17 inch roentgenographic film. The tray holding the cassette is then moved so as to underlie the lower extremities from approximately the region of the inguinal ligaments down to the midcalves or the ankles. A specially constructed graduated filter is used for exposure of the extremities to equalize the density of exposure to the thighs and legs. This is also attained by leaving a sheet of paper under the lower film in the cassette. A 50 milliliter Luer-Lok syringe is filled to the 40 or 45 milliliter mark with urokon sodium, which is diluted with an additional 10 or 15 milliliters of saline, the syringe being tilted back and forth until the medium is well blended with the saline.

Before the next injection is made, the position of the needle is checked by aspirating blood into the saline-filled syringe. The 50 milliliter syringe is then attached to the tubing, and the total quantity of diluted opaque material is injected. This injection should be made steadily at such a rate that the total time of injection is 10 to 15 seconds, giving a slow, continuous injection. The roentgenogram is made at the end of the injection. By this means, the arteries of both lower extremities in most cases are depicted down to the midcalves or even to the ankles (Fig. 1c and d). Figure 2c and d show the result of a slow injection through the lower needle recorded on 2 separate cassettes.

Timing the exposure. One of the problems in demonstrating the arteries of the legs by means of translumbar aortography is the question of timing the exposure so that the roentgenogram is not made before the opaque material has arrived at the lowest point one wishes to depict. By use of the aforementioned 50 milliliter syringe containing 55 or 60 milliliters of diluted opaque material, complete filling of the arterial tree of the lower extremities usually is obtained. As already indicated, such an injection takes up to 15 seconds, and this time almost always allows for filling of collateral arteries beyond the obstructed segments. Occasionally, a longer time is needed, as in Figure 3. In this instance, the time of arrival at the ankles of a tracer dose of radioactive urokon sodium injected into the lower abdominal aorta, as determined by means of a scintillation counter, was 19 seconds. A 60 milliliter dose of urokon sodium was then injected over a period of 15 seconds; 4 seconds later, the roentgenogram was made and satisfactory opacification of the arteries of the lower extremities was obtained. (In 2 patients without any areas of total segmental vascular obstruction, we found the circulation time from the lower portion of the aorta to the ankles to be less than 10 seconds by means of tracer doses of radioactive urokon sodium.)

A simpler method of determining the circulation time from the lower abdominal aorta to the lower part of the legs may be by the use of a reflector type of oximeter ("cyclops" oximeter) attached to the leg, perhaps over the shin, and injection of an indicator dye such as methylene blue through the lower needle in the aorta. We have not had the opportunity to try this idea, but according to Wood it may be practicable.

COMMENT

Approximately 25 deaths and 40 serious complications following translumbar aortography have been reported. In all cases in which the site of injection was mentioned, the injection had been made at, or just above, the level of the renal arteries.

Crawford and associates, as the result of differential studies of renal function done before and after aortography, stated that an upper limit of 25 milliliters of 70 per cent urokon sodium appears to be a safe dose

a

b

c

d

FIG. 2. a, Roentgenogram after injection of a small amount of radiopaque material through a needle placed in the aorta at the level of the twelfth thoracic vertebra. It is obvious that it will be possible to place a second needle in the aorta below the level of the renal arteries; however, due to dilution secondary to runoff, the sharp constriction found in the lower part of the aorta is not obvious. b, After a small injection into the aorta through a needle placed well below the renal arteries. The sharp constriction of the lower part of the aorta is obvious. c and d, Although a long cassette was not used, it is clear that slow injection of radiopaque material into the aorta through the needle seen in "b" has resulted in excellent visualization of arteries in pelvis and thigh.

when the injection is made at or above the level of the renal arteries. They considered that 15 to 25 milliliters of this medium was an adequate and safe dose for excellent aortography and that, by proper utilization of equipment and timing, the abdominal aorta and the major vessels of the lower extremities could be satisfactorily visualized. Thus, they concluded that larger amounts were unnecessary and potentially harmful,

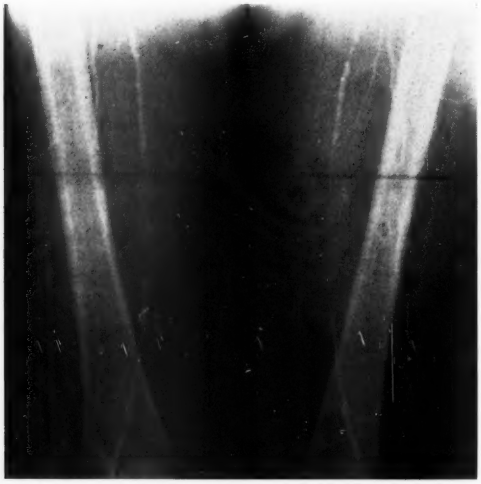

FIG. 3. Roentgenograms taken with the aid of a 36 inch cassette. The injection was made via a needle in the aorta well below the renal arteries. Despite bilateral segmental occlusion of the superficial femoral arteries, slow injection of approximately 60 milliliters of urokon sodium (approximately 55 per cent iodine concentration) gave excellent visualization of the arterial system of both lower extremities down to the ankles. (See text for use of radioactive tracer in this case.)

particularly when given as multiple injections. Mention should be made here of the investigations of Gaylis and Laws, who pointed to the possible dangers of intramural arterial injections, but this is probably a somewhat uncommon, although definite, predisposing cause of serious complications.

It is evident, then, that the site of injection is an important factor. Crawford and co-workers stated as follows: "The needle should enter the aorta at a level to prevent direct injection into a vital artery. This could be *theoretically more safely accomplished by injecting below the renal arteries*[1] since the major abdominal branches arise above this level. This is impractical, however, because occlusive lesions frequently arise at or extend up to the renal arteries and, secondly, the relationship of the major arteries to an aneurysm may be the indication for the study in the first place. Consequently, it will be necessary to inject above these vessels in most instances and this can be accomplished by piercing the aorta opposite the twelfth thoracic vertebra."

De Reus and Vink maintained that aortography always should be performed when angiographic examination is necessary in arterial circulatory disturbances of the extremities, because the terminal portion of the aorta and the iliac arteries may be diseased as well as the femoral arteries, and because collateral circulation for blocked superficial femoral arteries may arise from the pelvic vessels. They even contended that femoral arteriography should be abandoned. They advocated puncture of the aorta at the level of the third lumbar vetebra, distal to the large branches to the abdominal organs; they injected 40 to 50 milliliters of a 70 per cent solution of di-iodon in 4 seconds, preferably under manual control.

As we have indicated, once the aorta has been evaluated after injection through a "high" needle, it is easy to place a needle into the aorta below the level of the renal arteries, provided the aorta is not obliterated or unduly tortuous in this region or is not the site of an aneurysm. Our experience in several hundred cases shows that slow injection of a slightly diluted opaque material,

[1]Our italics.

even in fairly large quantities, done below the level of the renal arteries is capable of producing excellent arteriograms of the pelvis and legs with complete safety. Although we are indebted to Edward A. Edwards, of Boston, for suggesting to us a slow as opposed to a fast injection, we do not agree with his statement that, "I am much opposed to the proposition that aortography is to be preferred to bilateral femoral arteriography; the hazards of aortography are so much greater." It is our belief that this statement is true only when the entire examination is performed through one needle placed at, or above, the level of the renal arteries. Van Dongen is of the opinion that arteriography is accompanied by fewer complications when performed by the method of aortography than when it is done through the femoral artery.

By use of this slow injection method, we have on many occasions given as much as 100 milliliters of a 70 per cent solution of urokon sodium (in 2 or more injections) through the needle placed in the aorta well below the renal arteries, without any complications. However, it must be reiterated that the first injection, made through the needle that enters the aorta at approximately the level of the twelfth thoracic vertebra, should utilize as small a quantity of opaque material as possible, preferably 15 milliliters or less. Furthermore, we do not wish to create the impression that radiopaque materials should be injected into the lower abdominal aorta with a sense of abandon. We wish to stress the point that all our remarks relating to the apparent safety of infrarenal injections imply that the patient is in the prone position. Paraplegia has occurred in human beings when aortography has been performed with the patient in the supine position.

The method we have described is also simpler than other methods of outlining the arteries in the pelvis and lower extremities in that it does not require complicated or irritating methods of changing multiple cassettes during, and immediately after, the injection. It also has the advantage over femoral arteriography of evaluating the circulation in both legs at once, as well as of depicting the lower part of the aorta and the pelvic arteries.

SUMMARY

A method of aorto-arteriography has been described that is believed to be simpler and safer than most other techniques used. The two main safety factors are the insertion of a needle into the aorta below the level of the renal arteries and an extremely slow rate of injection. The main advantage in simplicity is the fact that use of a slow injection does away with the need for multiple cassettes, which must be changed in a short time. The slow injection achieves the same end as does a multiplicity of roentgenograms following rapid injection. This method might be called "replacement aorto-arteriography," because the blood in the main arterial channels, in effect, is replaced by radiopaque material.

REFERENCES

1. Astle, W. E. C., and Wallace-Jones, D. A simple radiological technique for femoral arteriography. Brit. J. Radiol., 1953, 26: 658.
2. Crawford, E. S., Beall, A. C., Moyer, J. H., and De Bakey, M. E. Complications of aortography. Surg. Gyn. Obst., 1957, 104: 129–141.
3. Edwards, E. A. Discussion. Surgery, 1957, 41: 163.
4. Gaylis, H., and Laws, J. W. Dissection of aorta as a complication of translumbar aortography. Brit. M. J., 1956, 2: 1141–1146.
5. Langsam, Martin, and Wilensky, N. D. An apparatus for automatic introduction of radiopaque media in translumbar aortography. Surgery, 1954, 36: 777–780.
6. Reus, H. D. de, and Vink, M. A report on the diagnosis and surgical treatment of peripheral obliterating arterial diseases. Arch. chir. Neerl., 1955, 7: 105–123.
7. Rogoff, S. M. Technique of serial long film angiography in arteriosclerosis obliterans. Am. J. Roentg., 1956, 76: 787–800.
8. Seldinger, S. I. Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta radiol., Stockh., 1953, 39: 368–376.
9. Van Dongen, R. J. Serie-aorto-arterio-flebografie; Apparatuur en werkwijze. Ned. tschr. geneesk., 1956, 100: 3718–3727.
10. Wood, E. H. Personal communication to the authors.
11. Wylie, E. J., and McGuinness, J. S. Recognition and treatment of arteriosclerotic stenosis of major arteries. Surg. Gyn. Obst., 1953, 97: 425–433.

THE EMBRYOLOGIC DEVELOPMENT AND DESCENT OF THE TESTIS IN RELATION TO CONGENITAL HERNIA

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CUMULATIVE DATA of the undescended testis emphasize the increasing need for the surgeon to be familiar with the origin, development, and descent of the testis; for without such knowledge abnormal variants in the migration of the reproductive organs may be present unexpectedly, causing confusion as to the proper surgical procedure that should be employed for their correction.

The embryologic development of the testis in its evolutionary descent may be divided into three distinct phases: (1) the intra-abdominal or supracanalicular, (2) the trans-abdominal or intracanalicular, and (3) the extra-abdominal, infracanalicular, or scrotal.

THE INTRA-ABDOMINAL PHASE (FIG. 1)

When the embryo is a three layered disk, which occurs at the third or fourth week, the coelomic cavity is formed from splitting of the mesoblast into visceral and parietal layers. The import of this embryologic unit is that the urogenital fold arises from invagination of the posterior wall of the coelomic cavity, developing in sequence after degeneration of the pronephros. The urogenital fold divides into the genital fold medially and the mesonephric fold laterally. These folds are separated except cranially and caudally but in their midportion each has a mesentery which unite to form a common mesenteric attachment to the posterior wall. The mesentery of the genital fold becomes the mesorchium in the male and the mesovarium in the female. At the same time another change takes place in which the medial and lateral reproductive grooves of the genital fold press inward just at the boundary between the mesenchyme and epithelial growth greatly narrowing the mesenteric attachment, but the grooves never meet.

The urogenital fold consists of two organs of diverse function but recognized initially as a single system owing to the facts that (1) they have a common mesodermic origin, (2) some of the excretory ducts are converted into ducts of genital organs in the male, and (3) these ducts are superadjacent to the urogenital sinus and to the primitive cloaca.

Mesonephric fold. Early in the second month of development of the human embryo, the mesonephros (wolffian body) is at the height of its growth. It extends from the fifth cervical to the fourth lumbar segment. It contains the mesonephric tubules, the excretory mesonephric duct, the mesenteric portion, and the muellerian duct which is the last component formed. This duct arises from the initial diminutive tubular growth formed by independent outgrowth of the blind end of this invagination on the lateral ridge of the mesonephros. Similarly, by the end of the second month of fetal life the upper cranial five-sixths, extending from the sixth to the twelfth thoracic segments of the mesonephros, has undergone atrophy; the persisting caudal portion, about one-sixth, extends from the first to the third lumbar segments. The latter one-sixth is divided into epigenitalis tubules connecting the testis to the epididymis and paragenitalis tubules which do not connect with the testis.

Caudalward, the undivided urogenital folds of the two sides meet on the dorsomedial surface of the urogenital sinus and fuse to form the genital cord. Contained in the common sheath of the genital cord are the caudal ends of the mesonephric and muel-

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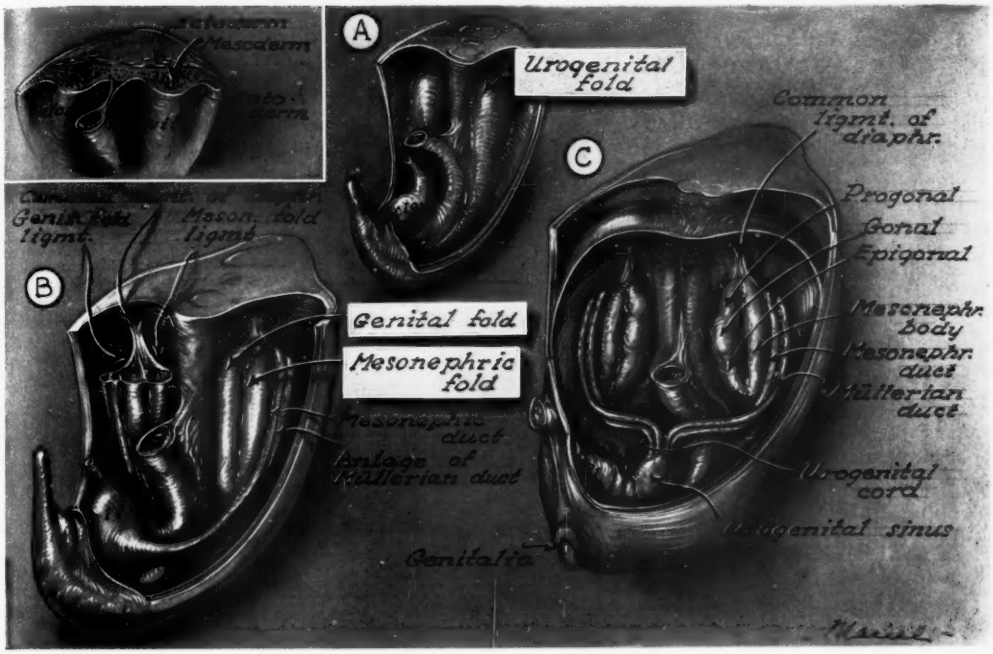

FIG. 1. Intra-abdominal, embryonic undifferentiated phase.

lerian ducts. Subsequently, in the male, the genital cord unites with the posterior wall of the bladder. In the female, however, the genital cord remains distinct from the bladder, and the space between constitutes the vesicouterine pouch. In the male fetus of the third month, the muellerian ducts are undergoing atrophy. By this time, the process of sexual differentiation is recognizable on close examination. All that remains of the muellerian ducts in the adult male are their fused terminal or vaginal segments forming the sinus pocularis or uterus masculinis of the urethra. The fimbriated ends of the muellerian ducts persist as sessile hydatids on the testes.

During the second month of fetal life the urogenital folds which lie parallel to the vertebral column become displaced laterally by the growing suprarenal bodies, stomach, intestines, and spleen; but caudal to the metanephros, the spreading force ceases and the vertical medial plane of the mesonephric and muellerian ducts is not altered. As a result of the displaced urogenital folds there occurs a characteristic bend at their caudal ends.

The mesonephric duct, which basically is the continuation of the pronephric duct, is concerned principally with the formation of certain male genital structures: the epididymis, paradidymis, seminal vesicles, and vas deferens. The ureter also arises from a diverticulum of this duct. In contrast, the muellerian ducts are related to the development of the uterus, broad ligaments, and fallopian tubes.

Genital fold. The genital fold consists of four parts: progonal, gonal, epigonal, and anlage of its mesentery. The epigonal is the largest, is much longer in the male, and during its regression forms part of the ligamentum testis. At this stage of development, the gonad has 3 ligaments: (1) the genital portion of the diaphragmatic ligament, (2) the mesorchium, and (3) the ligament pro-

pria or testicular ligament which is formed by the merging of the epigonal portion of the genital fold with the mesorchium.

The diaphragmatic ligament of the mesonephros continues to degenerate until it becomes the mesentery of the spermatic artery. The urogenital folds which are displaced laterally by the rapid growth of the intra-abdominal organs and the metanephros, but the mesonephric and muellerian ducts retain their former midline position.

Simultaneous with the change in the position of the urogenital fold a budding outgrowth appears at the first bend or tubar portion of the mesonephros. This growth bud is the primordium of the inguinal fold. It is directed laterally, destined to reach a similar bud arising from the lateral abdominal wall. Incidentally, no anterior abdominal wall exists at this stage of fetal development. The inguinal fold continues to grow inferolaterally until it meets the inguinal crest of the lateral abdominal wall which is growing cephalad. The inguinal fold contains a cord of compact mesenchyme which terminates at the internal abdominal ring, formerly the inguinal crest, and the site of the future exit of the testis from the abdominal cavity. The testicular ligament, connecting tubar portion of the mesonephros, and the inguinal fold constitute an uninterrupted cord extending from the inferior pole of the testis to the anterior abdominal wall. The intra-abdominal gubernaculum is therefore composed of 3 articulated links: (1) the testicular ligament, (2) the tubar or connecting portion of the mesonephros, and (3) the inguinal fold.

Evolution of the testis (*Fig. 2*). The development of the indifferent reproductive gland (gonad) begins about the fifth or sixth week, which is before the urogenital ridge divides into the mesonephric and genital folds. It begins as a strip of epithelium over the medial portion of the urogenital fold. At first the epithelial strip is composed of two layers of cells distributed uniformly over the mesial surface of the fold, but which soon becomes multilayered. In contrast, on the lateral surface of the fold there is no metaplasia of the epithelium. The region of the multilayered epithelium represents the reproductive gland area. At this stage there are no sharp boundaries between the thickened and nonthickened portion of the gland.

The next evolutionary step is the stage of epithelial ingrowth into the interior of the urogenital fold. This growth process compresses the loose mesenchymal tissue of the fold increasing its density but remaining sharply defined from the ingrowing epithelium. The growth of the reproductive gland area forms a solid mass. As soon as this growth reaches one third of the dorsoventral diameter of the urogenital fold the formation of the genital fold begins. At this phase, the boundary between the mesenchyme and epithelial growth is narrowed by the lateral and medial reproductive grooves. The mesonephric tubules are displaced laterally by the germinal epithelial mass.

The maximal extent of the reproductive gland is from the sixth thoracic to the second sacral segment. A faster elongation of the trunk cephalad, in contrast to the slower growing gonad, produces a relative shift of the latter in a caudal direction until the sex gland lies 10 segments below its level of origin, at the boundary between the abdomen and pelvis. Consequently, there is no internal descent of the testis. The change in the position of the testis is attributable to the growth and degeneration processes which proceed simultaneously, consecutively, and selectively.

THE TRANSABDOMINAL OR CANALICULAR PHASE (FIG. 3A)

While the inguinal fold with its mesenchymatous cord is growing in the direction of the lateral abdominal wall, another outgrowth, the inguinal crest, which is in the same horizontal plane appears on the lateral abdominal wall. The latter is directed medially toward the inguinal fold. The point at which these knoblike outgrowths meet marks the future site of the abdominal inguinal ring which is the internal entrance to the

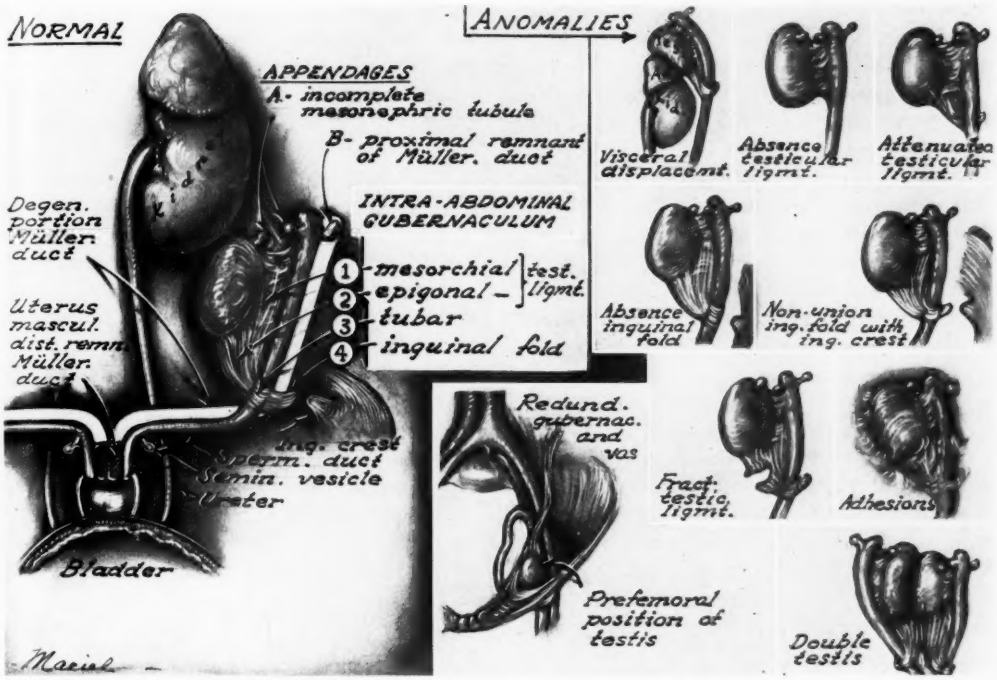

FIG. 2. Intra-abdominal, embryonic differentiated phase.

inguinal canal. Coincidentally, another coordinated embryologic process is taking place in which the lateral abdominal wall begins the phase of fascicular differentiation. Within the inguinal crest is a cord of compact mesenchyme, comparable to that in the inguinal fold, which extends caudalward into the groin. The abdominal wall in the process of growing ventrally to form the anterior abdominal component envelops the gubernacular cord, creating a canalicular space, the inguinal canal.

Arey and Patten have shown that the fibers of the primary myotome of the abdominal wall run in a transverse direction until differentiation into the adult muscle begins. Individual muscle masses are formed from the primary myotome by its splitting vertically and tangentially. After each muscle undergoes rotational adjustment, each unit fuses with its counterpart to form the adult abdominal wall. Aponeuroses and fascias form as "degenerations" of the parent muscle.

During the development of the anterior abdominal wall, loops of intestines which were formerly in the exocoelom begin to occupy the body cavity. Consequently, the coelomic cavity must become large enough to accommodate this additional bowel. The cavity develops by enlargement of the sagittal diameter, which means that the interval between the anterior and posterior abdominal walls is increased. As the anterior abdominal wall becomes progressively separated from the posterior abdominal wall, the testis is consequently drawn away from the wall. Since the testis is attached to the anterior abdominal wall through the chorda gubernaculum, it first becomes taut, and as the tension on the gubernaculum increases the long axis of the testis is rotated from its former vertical to a horizontal position. Coincident with these rotational changes the

testis moves in the direction of the abdominal ring, in preparation for its descent through the inguinal canal.

The gubernaculum in its caudal progress consists mainly of mesenchymal tissue but it steadily increases in density. In its passage through the canal the testis is followed by the spermatic cord which receives contributions from the respective muscle layers. The nonstriated muscle fibers of the gubernaculum are the source of its contractile function, so important in testicular migration through the inguinal and scrotal canals. These fascicular fibers are derived from subperitoneal areas in the evolutionary course of the plica gubernatrix.

Actual descent of the testis, which represents the second phase of testicular migration, begins with its entrance through the internal abdominal ring into the newly developed inguinal canal. Normally, this transitional phase occurs at the seventh fetal month. Sonneland attributes the downward progression of the testis through the inguinal canal to the following forces acting jointly or independently: (1) intra-abdominal pressure, (2) intramuscular pressure due to contraction of the muscles draped around the canal, and (3) guidance and active contraction of the smooth muscle of the chorda. As yet there is no accurate means of assessing the role played by these respective factors.

The peritoneal component of the gubernaculum remains constant, but in the formation of the inguinal canal there occurs an additional coexisting relationship with the peritoneum communis. A plica of peritoneum is traceable from the earliest position of the testis beginning at its inferior pole adjacent to the mesorchium and retains its identity until the testis reaches the scrotum. As the mesenchymal strands of the gubernaculum grow through the inguinal crest they become enveloped by the strata of the abdominal wall forming the conus vasculosus which in turn is undergoing selective differential growth. This process continues until the ultimate formation of the inguinal canal. The resultant evaginated pocket of peritoneum has initially a wide neck to preclude too rapid circumferential narrowing of the internal abdominal ring, which might impede the descent of the testis. With increased density of the parietal wall and coincidentally the attenuation of the coverings of the spermatic cord, the neck of the peritoneal pouch becomes smaller, gradually conforming to the predetermined canalicular growth motif. This phase of the continuity of the peritoneum and its relationship to the gubernaculum in the formation of the inguinal canal and the saccus vaginalis have been notably vague in texts of embryology. The accompanying illustrations have been designed to resolve much of the conjectural aspects of the descent of the testis and at the same time to retain the former perspective of the intimately related parietal components of the inguinal canal.

EXTRA-ABDOMINAL OR SCROTAL PHASE (FIG. 3B)

The anlage of the scrotum is the pubic apron. It should be recalled that the fibroblasts of the pubic apron are in continuity with those of the inguinal fold through the intermediary intracanalicular gubernaculum. At the end of the third fetal month this apron of subcutaneous tissue can be recognized above the root of the penis and lying in front of the symphysis. The prepubic apron has simultaneously undergone certain morphologic changes; the tissues of this area have become swollen and there is proliferation of the fibrocellular elements. It has been postulated that these rapid cellular changes may be influenced by the sex hormone. It has also been observed that the tissue growth lateral to the genital tubercle extends toward the perineum providing the sequential background for the formation of the scrotum.

More important clinically at this stage is the origin and development of the saccus vaginalis. Its relationship to the plica peritoneum of the gubernaculum has created diversity of opinion which still is not com-

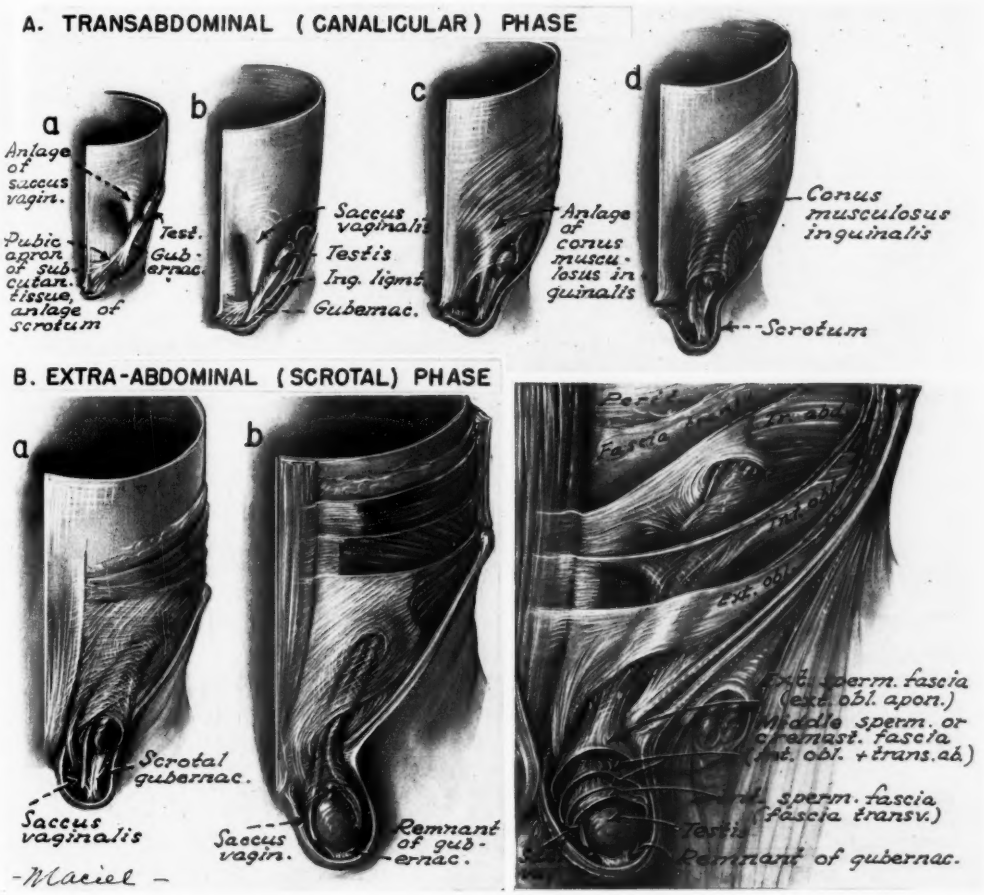

FIG. 3. A, Transabdominal (canalicular) phase. B, Extra-abdominal scrotal phase.

pletely resolved. However, consonant with other similar embryologic processes it would seem illogical to think of the saccus of the communis peritoneum and the parietal peritoneum (the latter a constant element of the gubernaculum) other than a composite integrated peritoneal unit from the beginning of the urogenital fold and continuing as a progressive caudal growth. Similarly, the same developmental process applies to the coverings of the spermatic cord which can be identified as attenuated elements of the canalicular fasciomuscular wall.

It should be recalled that at this period of fetal development the scrotum is diminutive, shallow, and without pendulous characteristics. Consequently, no appreciable demarcation exists between the scrotum and the inguinal canal during their early codevelopment. Simultaneously, as these related structures progress caudalward, the vaginal process of the peritoneum gradually becomes elongated and surrounded by the anterior abdominal wall which is destined to form the coverings of the inguinal canal. During these protean changes, the testis has constantly remained extraperitoneal, adja-

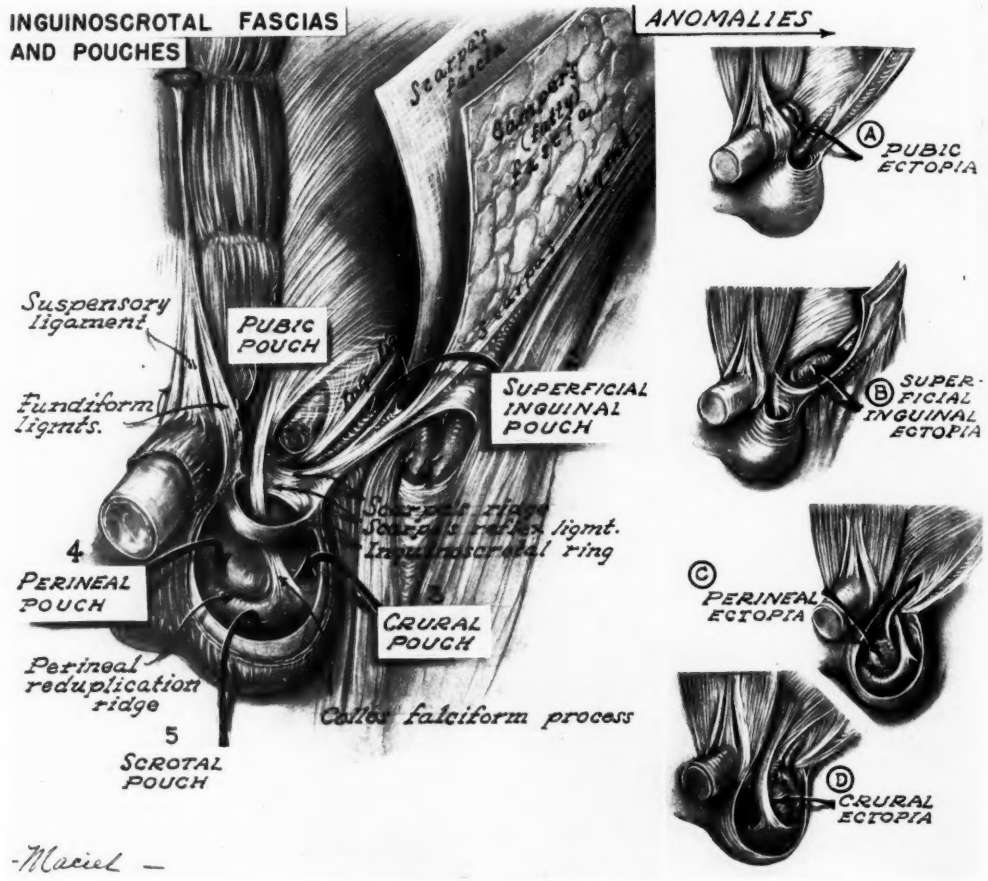

FIG. 4. Inguinoscrotal fascias and pouches.

cent but adherent to the peritoneum, a relationship beginning with its origin in the genital fold. In its progress downward, concomitant with the growth of the scrotum the former peritoneotesticular relationship is maintained. Thus, descent of the testis represents a correlative growth process, peritoneal, gubernacular, and parietoscrotal.

The direction and ultimate position of the testis after it enters the scrotal pouch are attributable to the conjoined fascial arrangements and their relationship to the scrotal gubernaculum (Fig. 4). The precise reason for the testicular arrest in its descent in the scrotum or why it deviates into the pubic, superficial inguinal, perineal, or crural pouch is not known. However, several explanations have been advanced for these ectopic positions: (1) Lockwood postulated gubernaculum tails, one extending into each pocket. This concept apparently has no embryologic or anatomic basis. (2) Abnormalities of the fascial planes of the scrotum explain the development of the scrotal pouches and may influence the direction of the testis by reason of inconstant fascial variants. (3) Weakness of the gubernaculum with possible increased resistance of the cremaster or cord elements may play a role in testicular maldescent.

It has been observed clinically, particularly in huge scrotal hernias that the spermatic cord becomes tremendously elongated until the testis may reach to the patient's knees. While this is an insidious process it is illustrative of the extent of accommodation the elements of the cord will undergo in adjusting to an inordinate situation.

DISCUSSION

Seldom does the surgeon manifest interest in embryology except where it has direct clinical application. Snyder found that 1 hernia in 15 (6.6 per cent) repaired in children is accompanied by an undescended testis and that 2 per cent of full term infants have imperfect obliteration of the process vaginalis at the internal ring. McCutcheon's figures of undescended testis were considerably higher, finding 192 in 2,132 (9 per cent) boys under 15 years of age and 12 (1.1 per cent) in 1,066 boys over 15. The incidence of cryptorchism in Drake's series was 4.2 per cent.

With these cumulative data on undescended testis it is almost mandatory that the general surgeon be familiar with the embryologic development and the normal versus the abnormal migration of the testis. Therapeutically, the recognition of a malposition of the testis is especially important in the last two phases of its migration since these phases comprise the true descent of the testis.

The abnormalities of the intra-abdominal phase of development of the testis are traceable to: (1) interference with the orderly development of the testicular ligament which arises from the epigonal portion of the genital fold and the mesorchium; (2) displacement of the inguinal fold, which extends from the tubar portion of the mesonephros to the inguinal crest—this may occur as a result of growing intra-abdominal organs as they are drawn into the coelom from the exocoelom; (3) redundancy of the abdominal gubernaculum allowing the testis to gravitate toward the femoral ring. If the former ring should become enlarged and

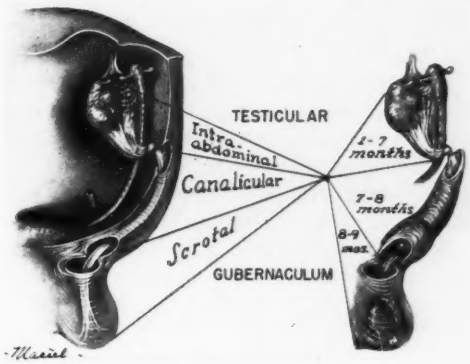

FIG. 5. The components of the testicular gubernaculum.

since it lies in a horizontal plane, a transfemoral ectopic testis may occur. Such an anomaly has been reported by Fauntleroy. It has been postulated that intra-abdominal adhesions perhaps could interfere with the migratory route of the testis but this possibility is extremely remote.

In the transabdominal phase which represents the first step of the true descent of the testis there are several factors to be considered: (1) the intra-abdominal pressure which aids in furnishing a thrusting force to a poised or engaged testis, (2) the intramuscular pressure from contraction of the parietal components of the inguinal canal, (3) the presence of the testis in the canal which may act as a foreign body with the normal response of the muscular elements to extrude it, (4) the stretch reflex which means that when a muscle is caused to contract, a stretch is applied to it, further enhancing its contraction, (5) the gubernaculum which is a fibromuscular cord has a dual function by acting as a guide and by exercising contractile power in pulling the testis caudalward through the canal. A less important factor is weakness of the elements of the gubernaculum which may produce an imbalance influencing testicular descent. An increased resistance of the cremaster muscle or tautness of the vessels of the spermatic cord may affect testicular progression. Therefore, in considering the eti-

ology of the undescended testis a retinue of closely related factors must necessarily be evaluated.

The extra-abdominal or scrotal phase consists of two steps (2): the first is limited to the space between the external ring and the inguinoscrotal ring which is perhaps 3.5 centimeters in length. This ring is composed of Scarpa's and Colles' fascias or variants of them arranged circumferentially. Should there be a stenosis of this ring, the testis may be directed either medially to the prepubic area or laterally to the superficial inguinal area. The second step occurs after the testis has negotiated the inguinoscrotal ring where its progress may be arrested by the perineoscrotal shelf. Again because of fascial anomalies the testis may be displaced either to the femoral area or to the perineum. If no fascial shelf is encountered the testis should proceed to its normal position in the dependent scrotal pouch. These ectopic positions of the testis are illustrative of the pitfalls that may be encountered by the surgeon in hernia repair, especially in infants and children. The chief motivating force of the testis after it clears the external inguinal ring is the gubernaculum.

Effort has been directed toward placing in full perspective the role of the composite or testicular gubernaculum. The components of the testicular gubernaculum are the intra-abdominal gubernaculum, the canalicular gubernaculum, and the scrotal gubernaculum, which are shown in continuity (Fig. 5). However, each segment respectively undergoes, at a predetermined evolutionary schedule, successive unit degeneration consonant with the position of the testis. In other words, the practical application of embryologic knowledge should supplement the presently required clinical and technical training in hernial surgery.

SUMMARY

1. The salient features of the embryologic development and descent of the testis have been reviewed.

2. The gonad phase as it progresses through growth and degeneration of the genital fold and the varying positions assumed by the testis have been discussed.

3. The development of anomalies of the testis and gubernaculum and their effect in influencing the progression of the testis through the inguinal and scrotal canals have been presented.

4. The common sites of ectopic testis have been illustrated, and some of the factors which have clinical application have been enumerated.

5. To clarify the relationship of the gubernaculum to the descent of the testis, the embryologic progression has been divided into 3 distinct sequential segmental phases.

6. It is important that the surgeon be endowed with the basic knowledge of the formation of the testis and the vicissitudes which may be encountered in reaching its destination.

REFERENCES

1. Arey, L. B. Developmental Anatomy. P. 391. Philadelphia: W. B. Saunders Co., 1940.
2. Burton, Claud C. A description of the boundaries of the inguinal rings and scrotal pouches. Surg. Gyn. Obst., 1957, 104: 142–150.
3. Drake, C. B. Spontaneous late descent of testis. J. Am. M. Ass., 1934, 102: 759–761.
4. Fauntleroy, A. M. Development of an inguinal hernia through the femoral ring after descent of testicle by same route. Ann. Surg., 1920, 72: 675.
5. Lockwood, C. B. Development and transition of the testes normal and abnormal, Hunterian Lecture. Brit. M. J., 1887, 1: 444–610.
6. McCutcheon, A. B. Further observation on delayed testis. Med. J. Australia, 1938, 1: 654–657.
7. Patten, B. M. Human Embryology. P. 298. New York: Blakiston Co., 1946.
8. Snyder, William. H., Jr. Inguinal hernia complicated by undescended testis. Am. J. Surg., 1955, 90: 325–330.
9. Sonneland, S. Gaylord. Undescended testicle. Surg. Gyn. Obst., 1925, 40: 535–545.

CLINICAL EXPERIENCE WITH INTRAMUSCULAR WARFARIN SODIUM (COUMADIN SODIUM)

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CLINICAL EXPERIENCE with the 4-hydroxycoumarin compound, warfarin sodium, has shown it to be an effective anticoagulant. A new preparation of sodium warfarin is now available for intramuscular and intravenous administration. This article deals with the intramuscular administration of warfarin sodium. Its use by the intravenous route has previously been described by Clatanoff and associates.

With the recent advances in cardiovascular surgery and the current concepts of cerebral vascular anticoagulant therapy, parenteral administration fills an important gap since the oral route may not be utilizable, and repeated intravenous administration may not be desirable.

METHODS AND MATERIAL

Determinations of the plasma prothrombin times were by the one stage method of Quick with thromboplastin (rabbit brain). Control prothrombin times were 12 seconds throughout, and the results are reported in percentage of normal. Blood was drawn daily at approximately the same time until definite patterns were established, and the administration of the anticoagulant was also at regular times in the afternoon. Optimal therapeutic levels were considered to be between 20 and 40 per cent of normal.

Seventeen patients received sodium warfarin intramuscularly. The first 4 patients were controls and did not have therapeutic indications for anticoagulation. Their diagnoses in the order of listing were angina pectoris, sarcoidosis, idiopathic exophthalmos, and rheumatoid arthritis. Patients numbered 5 through 17 had therapeutic indications for anticoagulation.

The first 4 patients received only 1 dose of sodium warfarin intramuscularly. The second group, 5 through 11, received their initial dose intramuscularly, and then continued to receive oral therapy. The final group had only intramuscular therapy.

The dosage was 1 milligram per kilogram with alterations depending upon the clinical status. Major changes in clinical status, i.e., operations and severe myocardial infarction, were reasons for substantially reducing dosage, and the changes are exactly the same by the various routes. It has been our experience that when anticoagulants are given immediately after surgery, the initial dose should be reduced by one-third to one-half of the usual dose.

RESULTS

Following intramuscular therapy, the initial prothrombin alteration is similar to that of oral or intravenous administration. A

TABLE I.—SUMMARY OF PROTHROMBIN DURING THE FIRST 48 HOURS

Cases	*Initial dose, mgm.*	*Prothrombin level— 24 hrs., per cent*	*48 hrs., per cent*	*Peak effect, hrs.*	*Prothrombin, 40 per cent or less*
1	75	57	24	48	36
2	60	35	17.5	48	20
3	50	40	16	48	24
4	75	37	15	48	24
5	75	46	19	48	30
6	40	52	18.5	48	36
7	50			36	36
8	35	52	23	48	36
9	35	34	35	24	24
10	50	62	17.5	48	36
11	60	42	30	48	24
12	65	62	13.5	48	36
13	50	52	27	48	36
14	40	52	34	48	48
15	65	45	24	48	48
16	50	89	26	48	48
17	45	40	17.5	48	24

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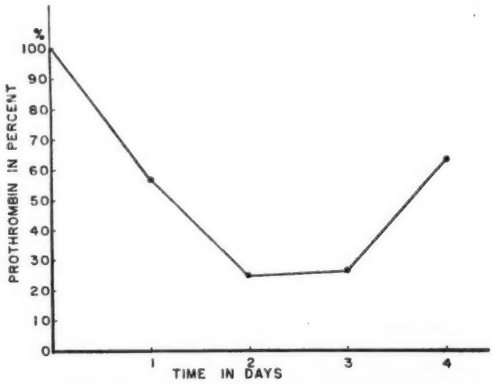

FIG. 1. Prothrombin response after a single injection of warfarin sodium.

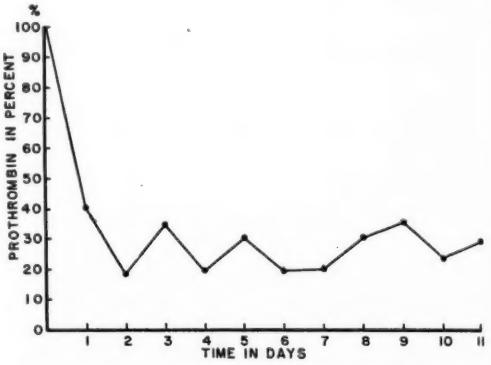

FIG. 2. Prothrombin response after multiple injections of warfarin sodium to a single patient.

typical example is seen in Figure 1. The second group of patients who received the initial dose intramuscularly with subsequent oral therapy are shown in Table I. The initial hypoprothrombinemia could be approximately anticipated and the subsequent change to oral therapy was without difficulty. The third group received warfarin only intramuscularly (Fig. 2.)

CONCLUSION

Intramuscular administration of warfarin sodium (coumadin sodium) was found to be as efficacious as administration of the anticoagulant by other routes, and there were no demonstrable side effects or detectable disadvantages. Single or repeated intramuscular doses can be satisfactorily employed.

REFERENCES

1. CLATANOFF, D. V., TRIGGS, P. O., and MEYER, O. O. Clinical experience with coumadin anticoagulants, warfarin, and warfarin sodium. Arch. Int. M., 1954, 94: 213.
2. QUICK, A. J. The clinical application of the hippuric acid and the prothrombin tests. Am. J. Clin. Path., 1940, 10: 222.

A QUANTITATIVE RELATIONSHIP OF WOUND TENSILE STRENGTH TO LENGTH

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IN THE COURSE OF OUR STUDIES on the acceleration of wound healing by cartilage (1), it was found necessary to evaluate certain variables which would have contributed to the error in the estimation of wound tensile strength. One of these variables proved to be the effect of wound length upon tensile strength. The results of this particular evaluation are presented here. Although these results were obtained with the rat, it is believed that, because of anatomic and dynamic similarities, the conclusions can be extrapolated to the human and in this manner provide assistance in the planning of incisions.

METHODS

The technique employed in the determination of wound tensile strength was that described in the report on the cartilage effect on healing wounds (1). It consists of the insertion of a latex rubber condom into the peritoneal cavity of the female albino rat (Sherman strain) which is to be tested. This condom is connected by means of a Y tube to a sphygmomanometer and to a set-screw positive pressure pump through which the pressure in the abdominal cavity can be precisely regulated. All of the wound tensile strength determinations reported here were done on the seventh day following closure of the particular abdominal incision under study. The sutures were removed immediately preceding the determination of the wound tensile strength, and the tests were done on freshly killed (intracardiac paraldehyde) animals.

All of the incisions, except the series labeled transverse, were longitudinal midline incisions. The standard length of the midline incision is 5.75 centimeters, and this was employed for all midline incisions in the present study, except when length was varied in order to evaluate its effect on tensile strength directly. The relative strength of transverse incisions was investigated by means of 4 centimeter longitudinal and transverse incisional pairs. In all paired studies, the incisions were of identical length. Identical numbers of sutures were always placed in transverse and longitudinal incisions of the same length.

In the series evaluating the effect of binding the abdomen, half of the rats studied were dressed with dry gauze held firmly in place over the wound with a tight adhesive binder. While this procedure is not strictly comparable to that employed in the postoperative human with an abdominal incision supported by a scultetus binder, there is, however, no doubt that support was afforded by the dressings. Some degree of tension was therefore removed from the suture line. This is the desired result when scultetus or other types of binders are applied to the postoperative abdomen.

In Tables I and II, it can be seen that the transverse and longitudinal incisions were compared by means of a "t" test on paired measurements. This was considered the proper statistical treatment since all rats were operated upon in pairs which were within 3 grams of each other in weight, had arrived in the Animal Care Department on

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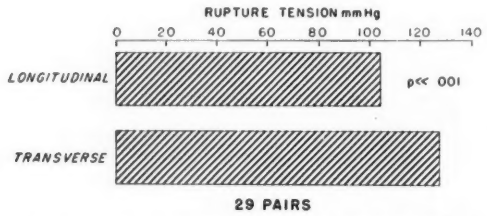

FIG. 1. The comparison between 7 day longitudinal and transverse incisional strength.

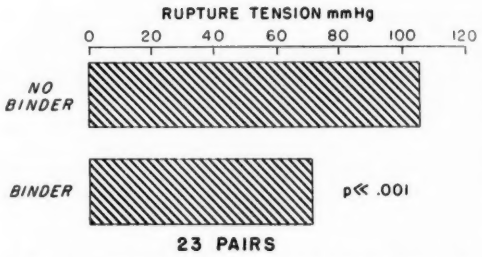

FIG. 2. The effect of supportive binding on longitudinal incisional strength.

the same day, and had occupied the same cage. The desirability and rationale of this method of pairing is described elsewhere (1). The same statistical methods were used in the comparison of the supported and unsupported wounds.

The relationship of incisional length to wound tensile strength has been expressed graphically in order to obtain a better understanding of the function which relates these two variables. The resultant experimental curve has been plotted on arithmetic and semilogarithmic paper. Its characteristics will be discussed.

TABLE I.—COMPARISON OF THE LONGITUDINAL AND TRANSVERSE INCISIONS

	No. of pairs	*Mean tensile strength, mm.Hg*	*Range*	$\hat{\sigma}_{\bar{x}_D}$	*t*	*p*
1. Longitudinal	29	104.2	75–144	5.04	4.63	<.001
2. Transverse		127.4	80–178			

TABLE II.—EFFECT OF BINDING ABDOMINAL INCISIONS

	No. of pairs	*Mean tensile strength, mm.Hg*	*Range*	$\hat{\sigma}_{\bar{x}_D}$	*t*	*p*
1. With binder	23	71.0	40–120	6.28	5.39	<.001
2. No binder		104.8	80–194			

TABLE III.—THE MEAN TENSILE STRENGTH OF LONGITUDINAL INCISIONS AT VARIOUS LENGTHS

	Length, cm.	*No. of observations*	*Means*	*Standard error of the means*
1.	2.75	18	175.30	8.49
2.	3.50	42	129.29	5.68
3.	4.00	21	121.70	7.74
4.	4.60	42	103.74	4.53
5.	5.75	101	98.70	2.99
6.	5.90	44	96.66	4.53

RESULTS

The effect of transverse incisions and longitudinal incisions on wound tensile strength. The results of this experimental evaluation are shown in Table I and Figure 1. It is evident that there is a marked increment in wound strength when the wound is placed in a transverse rather than in a longitudinal fashion. In the 29 pairs so tested, there were only 5 instances in which the longitudinal wound was the stronger of the two, and these differences were not nearly so large as were those obtained when the transverse wounds were the stronger. It is important to remember that all tensile strength determinations were made immediately after death. Therefore, any effect of the reflex tonic muscular action in line with the transverse incisions and perpendicular to the longitudinal incisions was eliminated. These measurements therefore represent an approach to the true strength of the two wound types, free of directional muscle pull effects. Any beneficial effect of the directional pull of muscles upon transverse incisions would be additive to the increased wound strength demonstrated to exist; also, the stability of suture positions is probably more favorable in transverse wounds, pulling as they do perpendicularly against fascial collagen.

The effect of abdominal binding upon wound tensile strength. Table II and Figure 2 show the results of this evaluation. The deleterious effects of external wound support upon healing are evident. In only 1 instance (out of 23 pairs) was an externally supported abdominal incision stronger.

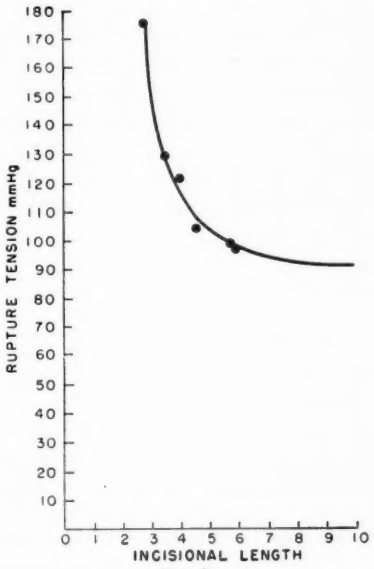

FIG. 3.

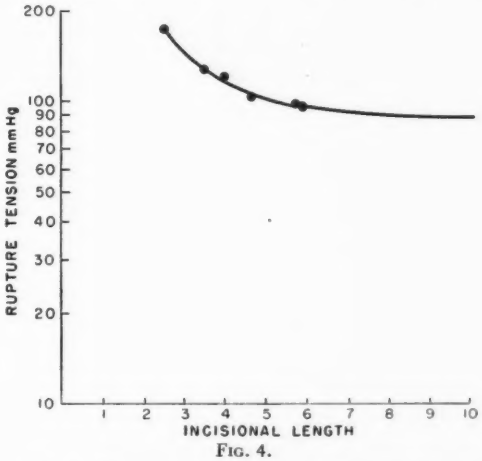

FIG. 4.

FIG. 3. Arithmetic plot of the relationship between tensile strength and incisional length.

FIG. 4. A semilogarithmic plot of the function relating tensile strength to incisional length.

The effect of incisional length upon wound tensile strength. This part of the study was carried out by measuring the mean tensile strengths of 6 midline incisional lengths, namely: 2.75, 3.5, 4, 4.6, and 5.75 and 5.9 centimeters. The mean tensile strengths of these varying wound lengths, together with the number of observations and the standard errors of the means, are reported in Table III; and the experimental curves relating incisional length to strength in arithmetic and semilogarithmic plots, respectively, are shown in Figures 3 and 4.

If the apparent plateau level (asymptote) of 90 millimeters of mercury is subtracted from each experimental value, and the resulting values are replotted semilogarithmically against the corresponding incisional lengths (Fig. 5) the resulting graph is strikingly linear. It is evident therefore that the function is uniexponential. The plateau value may be interpreted to represent the inherent strength of the wound itself at 7 days, without support from surrounding tissues. The exponential decrease in tensile strength which occurs as the incisional size is lengthened is governed by a constant presumably reflecting dissipation of wound support. The contribution of this support reaches its maximum when the incisional length becomes zero. Since this constant is undoubtedly contributed to by many force components, it is surprising that it can be fitted so well to a single exponential function.

Fitting the data by least squares, one obtains the function:

$$(T\text{-}90) = 646e^{-0.78L}$$

where T = tensile strength
L = incisional length

The applicability of this equation is attested by the determination of the zero intercept (i.e., when the incisional length is zero). Mathematically, in that case:

$$T\text{-}90 = 646e^{-(0.78)(0)}$$

or $T\text{-}90 = 646e^{0}$

or $T = 646 + 90$

$T = 736$ mm. Hg

This predicted rupture tension of the unoperated upon rat abdomen agrees closely with experimental observations we have made under those circumstances.

A simpler but less exact way of looking

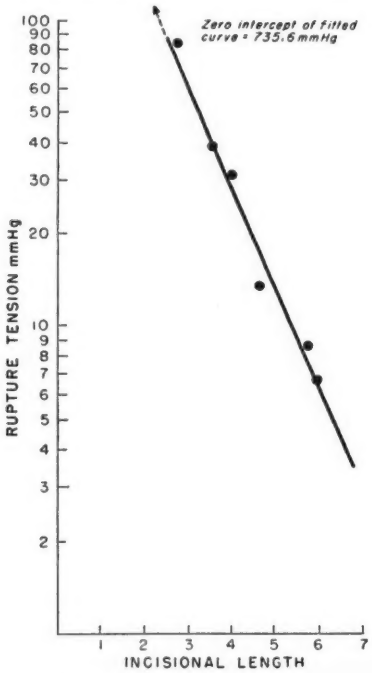

FIG. 5. The semilogarithmic plot after subtraction of 90 millimeters of mercury from all points (90 mm. Hg = plateau value).

at the relationship of incisional length to strength is given by considering the relationship as an inverse proportionality, namely:

$$TL = K$$

where T = tensile strength
L = incisional length
K = a constant

The approximation of the data to this function can be seen by considering the TL product for each point:

	T	L	K
1.	175.3 mm. Hg	2.75 cm.	482
2.	129.2 mm. Hg	3.50 cm.	453
3.	121.7 mm. Hg	4.00 cm.	486
4.	103.7 mm. Hg	4.60 cm.	476
5.	98.7 mm. Hg	5.75 cm.	567
6.	96.7 mm. Hg	5.90 cm.	570

It is seen that T and L have an approximate reciprocity until the curve begins to plateau sharply. This plateau begins only after incisional length has reached approximately 80 per cent of the maximum possible length of the incision (for the size of rat used in this investigation the average distance —approximate weight = 200 grams—between the ensiform and pubis was 7.0 cm.).

In other words, for incisions less than about 80 per cent of the total longitudinal distance available for an incision, one sacrifices strength with increasing length in an almost exactly reciprocal manner. Beyond this, the support of the transverse musculature and surrounding tissue rapidly becomes so negligible that the strength of the wound plateaus at a level only slightly less than those observed at incisional lengths of about 80 per cent total available length.

The clinical import of both the exact and approximate mathematical representations of the data is essentially the same: there is a remarkably rapid diminution of tensile strength as the incision is lengthened from zero. This can be seen most clearly by employing the more exact equation, viz.:

$$(T\text{-}90) = 646e^{-.78L}$$

By substituting a value of half the calculated strength of the unincised rat abdominal wall (735.6 mm.Hg), we can calculate the length of the incision which will produce a wound strength of half the original magnitude. Thus:

$$368 - 90 = 646e^{-.78L}$$

$$278 = 646e^{-.78L}$$

$$e^{-.78L} = .43$$

$$\text{or } L_{1/2} = .89 \text{ cm.}$$

In other words, a wound tensile strength of half that of an infinitely small incision is reached with a length of only .89 centimeter, this great reduction in strength having been brought about by an incision of only 12.7 per cent of the total possible length available.

DISCUSSION

Assuming that the anatomic and biochemical similarities between the rat and human permit application of these studies

to clinical situations, these experiments strongly reinforce one widely held idea (that transverse abdominal incisions heal more rapidly than longitudinal ones), definitely contradict another (that putting a wound at rest through external abdominal support is beneficial to its rate of healing), and offer considerable information regarding the effect of incisional length upon the tensile strength of healing wounds.

The superiority of transverse incisions appears particularly reinforced by these findings, since the test animals were dead, and the coapting action of the transverse and oblique musculature was therefore not operative. The interesting fact is that, nevertheless, the transverse wounds were much stronger. A rather convincing argument can therefore be made in favor of the use of transverse incisions in all patients exhibiting a less than ideal nutritional status, or in the aged at any time. Of course, it is obvious that other circumstances pertinent to the contemplated procedure, or to the particular patient under treatment, may well make a longitudinal incision preferable. Other factors being equal, however, transverse incisions are distinctly superior.

Binders unquestionably remove some tension from a suture line; and if a closure is precarious on that basis, their use is rational and justifiable. However, these data contradict the notion that such an action on the suture line will result in a stronger wound. Indeed, it appears that moderate tension (perhaps motion) will result in stronger wounds.

The studies on the relationship between the length and strength of incisions have shown that, in the case of longitudinal incisions, length and strength are reciprocal variables until the wound reaches 80 per cent of the total possible length, after which increments in length produce virtually no decrement in strength. Indeed, after approximately 90 per cent of possible incisional length is reached, there is no measurable decrease for all practical purposes, the rupture tension then being largely representative of the strength of the healing wound alone.

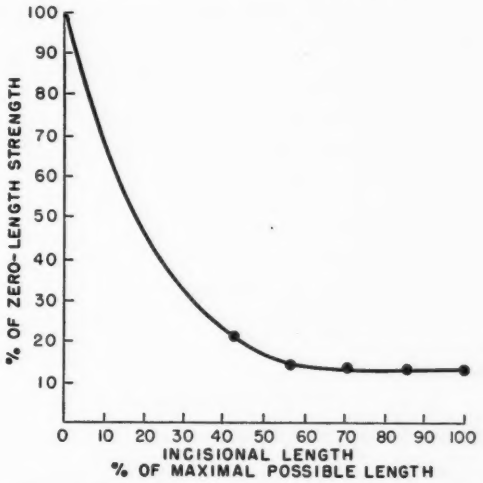

FIG. 6. The effect of incisional lengthening on the relative strength of wounds.

Figure 6 summarizes the effect of incisional lengthening upon the relative strength of the wound and demonstrates that, if one lengthens an incision from 50 to 100 per cent of the maximal possible length, the wound strength changes by an amount approximating 4.5 per cent of the zero length strength of the wound. Even an elongation from 40 to 100 per cent would cause a decrease of only around 12 per cent, while a change from 60 to 100 per cent would mean a negligible decrease of about 1.8 per cent! Since it is rare to make an abdominal incision of less than 50 per cent of the total available possible incisional length, the conclusion seems clear; viz., incisions which do not permit adequate exposure should be lengthened without hesitation in the realization that no significant reduction in wound strength will ensue.

No evaluation of the length-strength function has been made for other types of incisions. It appears likely that the same general graphical relationships will hold; however, it would be expected that both the point at which the plateau of the curve begins and the level of the plateau would be different.

It should be re-emphasized that these data are derived from rat experiments which are essentially miniatures of human operative circumstances. Extrapolation to the human situation appears reasonable since the basic anatomic and biochemical features are the same.

CONCLUSIONS

1. Transverse incisions are considerably stronger than midline ones.

2. Postoperative external abdominal support decreases the inherent tensile strength of wounds.

3. There is no appreciable decrease in wound tensile strength when abdominal incisional length is increased from 50 to 100 per cent of the maximal possible incisional length. Incisions for major abdominal operations should therefore be made as long as is necessary to eliminate completely any interference with exposure referable to incisional length, since such a practice will result in no significant decrement in wound strength.

4. These conclusions are based upon the assumption that the biochemical and physical characteristics of the abdominal wounds in the rat are sufficiently similar to those in humans to permit interpretive extrapolation of the experimental data to clinical conditions.

REFERENCE

1. Prudden, J. F., and Nishihara, G. The acceleration of wound healing with cartilage—I. Surg. Gyn. Obst., 1957, 105: 283.

THE EFFECT OF THE PROPERDIN SYSTEM UPON FIRST AND SECOND SET HOMOGRAFTS

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MEDAWAR showed, in his extensive study of skin homografts in rabbits, that the failure of homografts is a function of the host's immune defense mechanism. In a series of papers, Medawar (5–7) presented the following observations: (1) The second set homografts sloughed after a significantly shorter latent period than the first set homografts. (2) The second set homografts began to slough at the time of vascularization of the homografts. (3) The homografts are invariably destroyed by a reaction of the anaphylactic type.

These findings are in harmony with the present antibody formation and antigen-antibody reaction theory; these observations also point to the presence of a circulating antibody. To date, however, a specific circulating cytotoxic antibody against skin homografts or other tissue homografts has not been identified.

Recently, Pillemer and his associates have shown that normal human and other mammalian sera contain a protein, properdin, that is an integral part of the natural defense mechanism of blood (4, 8, 9, 11–13). Properdin is a beta-euglobulin with a molecular weight of about 20 times that of serum albumin and represents not more than 0.03 per cent of the total serum proteins. It is dependent for its action upon complement and Mg^{++}, and kills, lyses, or inactivates certain bacteria, protozoa, abnormal erythrocytes, phage, and viruses, in the absence of specific antibodies. Properdin has been found to differ from antibody in many respects. It combines with diverse and apparently unrelated substances, while antibodies are relatively specific in this respect. It is present in normal sera, while antibodies generally appear in serum in response to antigenic stimuli. It resides in fraction III-1 (Cohn), while antibodies are usually present in fraction II but also are found in fraction III. Properdin requires complement fraction C′1, C′4, and Mg^{++} for its combination with various agents. Antibodies have no such requirements for combination with antigen. Properdin-zymosan and certain other properdin-polysaccharide complexes inactivate C′3 specifically, while antigen-antibody complexes inactivate C′1, C′2, and C′4, with no effect on C′3. Thus properdin is distinct from antibody in the commonly accepted sense. Bactericidal antibodies, however, require complement for their activity and resemble properdin in this respect. Thus, properdin may be a primordial type of antibody. Since the properdin system is a new and relatively unexplored phase of immunity we became interested in its possible role in the field of tissue homotransplantation. This was of particular interest because the properdin system can be altered in laboratory animals by: (1) total body irradiation; (2) experimental hemorrhagic shock; and (3) by the administration of certain agents: zymosan, dextrans, levans, and other carbohydrate complexes, thus allowing controlled host properdin responses. Experiments were designed to determine whether the elusive antitissue antibody might be associated with the properdin sys-

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FIG. 1. The mean effect of a single intravenous injection of B-1355 dextran (100 mgm./kgm.) on the serum properdin titer in 5 rabbits.

tem and work was conducted to see what effect, if any, depression of the properdin system would have on the survival of rabbit skin homotransplants.

METHODS

The laboratory animals used in these experiments were 1 kilogram nonlitter mate albino rabbits. Periodic blood samples collected throughout the experiments were obtained by incising the marginal vein of one of the ears and collecting the blood in acid washed test tubes. Intravenous injections throughout the experiment were made in a suitable ear vein, usually the marginal vein, in the other ear.

A native dextran B-1355 was used to depress the properdin system; another native dextran B-512 was used as a control. These dextrans, B-1355 and B-512 were supplied by Pillemer. B-1355 is capable of removing or inactivating properdin C'3 in human serum and B-512 is completely inactive in this respect and was therefore chosen as a control. These dextrans were administered in a saline solution (20 mgm./c.c.) that was freshly prepared before use.

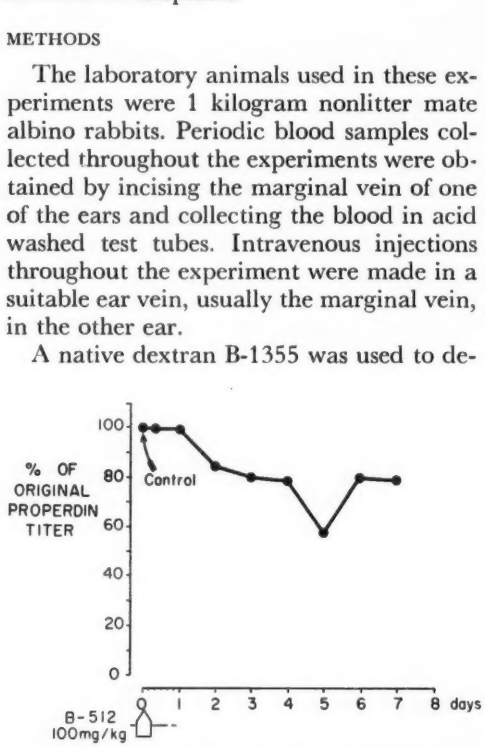

FIG. 2. The mean effect of a single intravenous injection of B-512 dextran (100 mgm./kgm.) on the serum properdin titer in 5 rabbits.

For the determinations of the properdin titers, 4 cubic centimeters of blood were drawn, allowed to clot for 1 hour, and centrifuged twice for 20 minutes at 3,000 revolutions per minute. The plasma was withdrawn, frozen, and stored in a deep freeze until the titers could be run. The properdin titers were determined by the standard technique described by Pillemer and done in his laboratory. The technique of doing the properdin titers will not be described as they have been published in detail by Pillemer (10).

At the time the properdin levels were done, a group of experiments were done centrifuging the samples at 35,000 g and comparing them with the noncentrifuged specimens. There was no significant difference in the properdin titers in the two groups and therefore the remainder of the samples were not centrifuged at 35,000 g.

In these experiments 3 series of animals were used. The first series was used to establish the effect of dextrans B-1355 and B-512 on the rabbit serum properdin titer in vivo. The second series was used to determine the effect of a depressed properdin system on the life span of first set rabbit skin homografts. The third series was used to determine the same effect on second set homografts.

In the first series, 10 rabbits were used. A control blood sample was drawn from each rabbit. One hour later each of 5 rabbits was injected intravenously with B-1355 (100 mgm./kgm.) and another group of 5 rabbits was injected with B-512 (100 mgm./kgm.). Four hours after injection, a blood sample was drawn from each rabbit. Thereafter

daily blood samples were drawn from all rabbits for a period of 7 days.

In the second series, 20 rabbits were used. The rabbits were paired up arbitrarily; one rabbit of each pair was designated as "active" and the other as "inactive." A control blood sample was drawn from each rabbit. The active rabbits were then injected with B-1355 (100 mgm./kgm.) and the inactive with B-512 (100 mgm./kgm.). After 24 hours, a blood sample was drawn from each rabbit and the rabbits were anesthetized with nembutal (0.5 c.c./kgm.). A skin area (10 by 15 cm.) was cleaned with clippers and depilatory powder. When the rabbits were sufficiently anesthetized, each pair was cross-homografted. Using modified aseptic technique, split thickness skin grafts, 2 by 4 centimeters, were cut according to the method of Hansen and Hubay (1). At the site of the graft, the remaining dermis was completely removed down to the panniculus carnosus and all blood vessels were ligated with No. 5-0 silk sutures. This area then served as the bed for the recipient graft. The graft was sutured into place with interrupted sutures of No. 5-0 silk and fastened centrally to the deep fascia with 1 or 2 sutures.

The homografts were observed daily. The dextrans B-1355 (100 mgm./kgm.) and B-512 (100 mgm./kgm.) were administered respectively to the active and inactive groups at intervals of 72 hours (see results), following the initial injection of the dextrans. Before each administration of dextran, a blood sample was drawn for the determination of the properdin titer. This procedure was terminated with the rejection of the homografts.

In a third series, 10 rabbits were used. The rabbits were paired up arbitrarily and each pair was cross-homografted. The homografts were observed daily until they were rejected. Three weeks after the first grafting procedure, and approximately 13 days after rejection, a blood sample was drawn from each rabbit. One rabbit of each pair was designated as active and was injected with B-1355 (100 mgm./kgm.), the other rabbit of each pair was designated as inactive and was injected with B-512 (100 mgm./kgm.). Twenty-four hours later each pair was cross-homografted a second time. Observations and blood samples of the second set homografts were made daily. Dextrans B-1355 and B-512 were administered respectively to the active and inactive groups of animals at intervals of 72 hours after initial administration of dextrans.

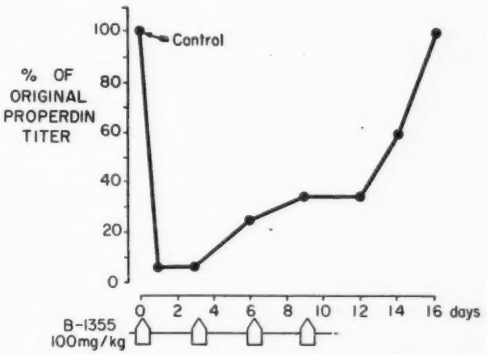

FIG. 3. The mean effect of multiple intravenous injections at 72 hour intervals of B-1355 dextran (100 mgm./kgm.) on the serum properdin titer of 10 rabbits. Homografts were applied on day 1.

RESULTS AND DISCUSSION

I. In the first series of experiments on the effect of dextrans B-1355 and B-512 on the

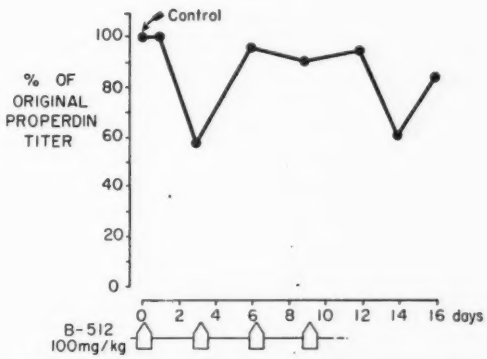

FIG. 4. The mean effect of multiple intravenous injections of B-512 dextran (100 mgm./kgm.) on the serum properdin titer of 10 rabbits. Homografts were applied on day 1.

TABLE I.—SURVIVAL OF HOMOGRAFTS

Treated with B-1355		*Treated with B-512*	
Rabbit	*Days*	*Rabbit*	*Days*
I_1	10	I_4	10
I_3	8	II_2	11
II_1	9	II_4	9
II_3	8	III_2	9
III_1	9	III_4	11
III_3	8	IV_2	16
IV_1	10	IV_4	8
IV_3	10	V_2	8
V_3	12	V_4	14
Average	9.3	Average	10.6

TABLE II. — SURVIVAL OF FIRST SET HOMOGRAFTS

Rabbit	*Days*	*Rabbit*	*Days*
1	10	2	10
3	6	4	9
5	7	6	6
7	8	8	6
9	8	10	8
Average	8	Average	8

TABLE III. — SURVIVAL OF SECOND SET HOMOGRAFTS

Treated with B-1355		*Treated with B-512*	
Rabbit	*Days*	*Rabbit*	*Days*
1	5	2	6
3	5	4	6
5	5	6	6
7	6	8	6
9	—	10	—
Average	5	Average	6

serum properdin level in rabbits, it was found that only B-1355 was capable of depressing the properdin titers significantly. In the 5 rabbits, each of which received a single dose of B-1355 (100 mgm./kgm.), the average properdin titers dropped within 4 hours to less than 7 per cent of their initial values and remained at this low level for 72 hours and thereafter rose to their initial values (Fig. 1). In 5 rabbits, each of which received a single dose of B-512 (100 mgm./kgm.), the average properdin titers did not change significantly (Fig. 2).

II. In the second series there were 10 rabbits in the active group; each rabbit received multiple doses of B-1355 (100 mgm./kgm.) at intervals of 72 hours. In this group, the properdin titers dropped to low values and in general remained at this level throughout the course of injections. Although there was more variation in the responses to multiple injections, 7 out of 10 rabbits had levels of 7 per cent of normal, and the remainder showed moderate depressions at 6 and 9 days respectively. Seventy-two to 96 hours after the last injection, the properdin titers were rising toward their initial values (Fig. 3).

In the second series of animals there were 10 rabbits in the inactive group and each rabbit received multiple injections with B-512. The properdin titers in this group did not change significantly throughout the experiment (Fig. 4).

Twenty rabbits were cross-homografted, 10 in the active and 10 in the inactive group. Two rabbits, one from the active and one from the inactive group, destroyed their skin homografts prematurely, so a complete observation could only be made on 18 homografts of the 20. The average time for rejection of the 9 homografts in the active group was found to be 9.3 days, and the average time for rejection of the 9 homografts in the inactive group was found to be 10.6 days (Table I). This is not thought to be a significant difference.

III. In the third series, 5 pairs of rabbits were homografted without receiving injections with dextrans. The average time for rejection of these 10 first set homografts was found to be 8 days (Table II).

Three weeks after the placing of the first set homografts, and approximately 13 days after rejection, the rabbits were started on a series of multiple injections with dextrans every 72 hours (one rabbit of each pair received B-1355, while the other received B-512). Each pair of rabbits was then cross-homografted again. During this procedure 1 rabbit died from anesthesia so that second set cross-homografting was completed in 4 pairs only.

In the 4 rabbits of the active group, the properdin titers were found to be depressed to less than 7 per cent of their initial values and maintained at this low level throughout the experiment (Fig. 5). In the 4 rabbits of the inactive group, the properdin titers were not found to be altered significantly (Fig. 6).

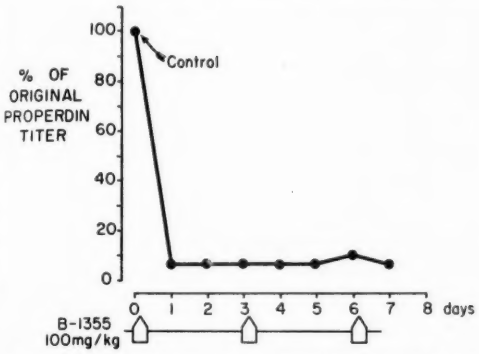

FIG. 5. The mean effect of multiple intravenous injections of B-1355 dextran (100 mgm./kgm.) on the serum properdin titer of 4 rabbits. Second set homografts were applied on day 1.

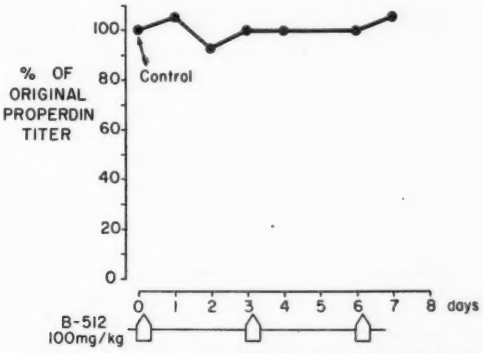

FIG. 6. The mean effect of multiple intravenous injections of B-512 dextran (100 mgm./kgm.) on the serum properdin titer of 4 rabbits. Second set homografts applied on day 1.

The average time for rejection of the second set homografts was found to be 4 days in the active group and 5 days in the inactive group. This difference was not thought to be significant and was similar to rejection times reported by Medawar.

It should be pointed out that, on the average, the homografts in the active and inactive group of the second experiment and the first set homografts in the third experiment survived about the same length of time (9.3 and 10.6 days respectively). Since these animals received treatment with B-1355, B-512, and no treatment respectively, it is concluded that the rejection time of skin homografts in rabbits was not prolonged by the administration of B-1355 (100 mgm./kgm.) or B-512 (100 mgm./kgm.) at intervals of 72 hours.

It should also be pointed out that the life span of the second set homografts of rabbits treated with B-1355 (100 mgm./kgm.) was not prolonged over the life span of the second set homografts on rabbits treated with B-512 (100 mgm./kgm.) at an interval of 72 hours.

It is apparent from these studies that first set and second set rabbit homografts were not favorably influenced when exposed to an artificially produced low properdin system. At the present time, the role of the properdin system in the rejection of tissue homotransplants needs further clarification although it would seem by this series of experiments and the experiments performed by Hubay, Persky, and Holden (2, 3) that alteration of the properdin system is not related to homograft survival. It is of interest that a globulin fraction of the blood concerned with natural immunity can be altered by the intravenous administration of high molecular weight polysaccharides.

SUMMARY

The effect of dextrans B-1355 and B-512 on the properdin system in rabbits was explored. It was found that B-1355 (100 mgm./kgm.) was capable of depressing the properdin system; B-512 (100 mgm./kgm.) was not found capable of altering the properdin system in rabbits.

When the properdin system was artificially depressed in rabbits with B-1355 (100 mgm./kgm.), the survival of the first set as well as the second set homografts was not found to be prolonged.

REFERENCES

1. HANSEN, F. C., and HUBAY, C. A. A simple method of cutting split thickness skin grafts from small animals. Proc. Soc. Exp. Biol., N. Y., 1956, 93: 506–507.
2. HUBAY, C. A., PERSKY, L., and HOLDEN, W. Preliminary experience with properdin and renal homografts. Surgical Forum; Clinical Congress 1957. Vol. VIII, pp. 618–622. Chicago: American College of Surgeons, 1958.

3. Hubay, C. A., and Persky, L. Properdin and renal homografts. Transplant. Bull., 1957, 4: 58–60.
4. Landy, M., and Pillemer, L. Increased resistance to infection and accompanying alteration in properdin levels following administration of bacterial lipopolysaccharides. J. Exp. M., 1956, 104: 383–409.
5. Medawar, P. B. The behavior and fate of skin autografts and skin homografts in rabbits. J. Anat., Lond., 1944, 78: 176–199.
6. Idem. A second study of the behavior and fate of skin homografts in rabbits. J. Anat., Lond., 1945, 79: 157–179.
7. Idem. Immunity to homologous grafted skin—III, the fate of homografts transplanted to the brain, to subcutaneous tissue, and to anterior chambers of the eyes. Brit. J. Exp. Path., 1948, 29: 58–69.
8. Pillemer, L., Blum, L., Lepow, I. H., Ross, O. A., Todd, E. W., and Wardlaw, A. C. Properdin system and immunity—I, demonstration and isolation of a new serum protein, properdin; its role in immune phenomena. Science, 1954, 120: 279–285.
9. Pillemer, L., Schoenberg, M. D., Blum, L., and Wurz, L. Properdin system and immunity—II, interaction of the properdin system with polysaccharides. Science, 1955, 122: 545–549.
10. Pillemer, L., Blum, L., Lepow, I. H., Wurz, L., and Todd, E. W. The properdin system and immunity—III, the zymosan assay of properdin. J. Exp. M., 1956, 108: 1–13.
11. Pillemer, L., Landy, M., and Shear, M. J. The properdin system and immunity—VII, alterations in properdin levels and resistance to infection in mice following the administration of tissue polysaccharides. J. Exp. M., 1956, 104: 707–725.
12. Wardlaw, A. C., and Pillemer, L. The properdin system and immunity—V, the bactericidal activity of the properdin system. J. Exp. M., 1956, 103: 553–575.
13. Wedgewood, R. J., Ginsberg, H. S., and Pillemer, L. Properdin system and immunity—VI, the inactivation of Newcastle disease virus by the properdin system. J. Exp. M., 1957, 106: 99–110.

INVESTIGATION OF TUMORS OF THE SKIN (EPIDERMIS) USING A HISTOCHEMICAL TECHNIQUE

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THE DIAGNOSIS OF TUMORS of any organ is achieved by the collation of data such as the macroscopic appearance of the growth, the known history of such tumors, and their histologic characters. When a particular tumor attracts early attention and is readily accessible to observation and treatment, its nature is more likely to be completely understood than those arising in deeply situated organs. In such cases the course of the growths in their late stages are often well known, but knowledge of their early characteristics depends on accidental discovery of examples followed by observation and special investigation such as x-ray examination and endoscopy. Skin tumors are, therefore, from the point of view of ease of study, in a peculiarly favorable position.

Because of this, a good deal is known about some skin tumors and, presumably because of the early and adequate treatment that can be provided here, the results of such treatment are relatively favorable. On the other hand the ease of treatment, particularly the surgical excision of the small nodule, has allowed the wholesale removal of small "tumors" of the skin so that their subsequent course is often quite unknown. The reflection that skin tumors were not as common in the days of our forefathers, when surgical interference was so serious a matter as to be a last resort, as they are said to be today, should make us query some of the otherwise unquestioned tenets of modern practice.

This implication that many of the small tumors are malignant and potential destroyers of both the region and ultimately the individual has had some support from histologic observations. The significance of histologic structure is arrived at by correlation of appearances with the clinical course of the condition; when this cannot be achieved easily the nature of a particular tissue is assumed from its similarity to others whose potentialities are known. This has been shown, in recent years, sometimes to be grossly fallacious; the criteria of malignancy in one tissue may be very different from those of another which, however, may seem similar.

Careful study of the different examples sometimes reveals distinct histologic differences but these require meticulous search and scrupulous integration of observations. Curiously, studies of this kind have proved fruitful in recent years even in the skin where such possibilities for research of this nature would not have been expected to exist, showing that there are always gleanings to be gathered even in the best-reaped fields.

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HISTORICAL NOTE

The discovery of the chemical carcinogens and their production in pure form—especially the condensed cyclic hydrocarbons and the azo dyes—have provided the majority of the material for experimental cancer research of the last 2 decades. Their application to the skin, as one of the easier methods of introducing them to a tissue in a controlled manner, has meant that much investigation has been carried out here. It has been possible to control dosage, time and extent of application, and the period during which the material is used. Work on the skin, therefore, has been in sharp contrast with, for example, that on the bowel.

TABLE I

Condition	*No. examined*	*Fluorescence of epithelial cells*
Normal skin	46	Bright and even
Warts	8	Bright and even
Irritated epithelium	12	Bright and even
Molluscum pseudocarcinomatosum	6	Bright and even
Sudoriferous adenoma	1	Bright and even
Squamous cell carcinoma	8	Absent
Basal cell carcinoma	5	Absent
Induced skin carcinoma (mouse)	5	Absent

Showing results of fluorescence staining in series of skin tumors investigated. The cells of the 18 malignant tumors failed to stain whereas those of the 15 hyperplasias stained in the same way as normal epidermis.

A study of the mode of action of carcinogens was made here at an early stage and it was found that the carcinogen united with the cells which were later to become neoplastic. This was shown in the cells of the epidermis with 3,4-benzpyrene and, later, 1,2:5,6-dibenzanthracene.

This type of observation has been made also with the azo dyes (4-dimethyl-aminoazobenzene) in the liver. Here again the carcinogen becomes attached to or incorporated in the liver cell. Sorof and Cohen have shown by differential high-speed centrifugation of liver cell homogenates, as well as electrophoretically, that the carcinogen unites with a protein complex of the soluble protein of the cytoplasm.

A further step was the observation that when a tumor (hepatoma) developed it did not contain any bound dye. Miller and Miller then showed that the protein complex, which had bound the dye in the normal cell, was missing from the malignant cell.

The problem was then approached from a different direction. Normal rat liver tissue was injected into a rabbit and, subsequently, rabbit serum was obtained. This united with liver tissue in histologic sections—apparently a clear example of an antigen-antibody reaction. This could be observed by producing a stain containing the rabbit serum component; the globulin was conjugated with a fluorescein compound (amine) and its localization was then easily seen under ultraviolet light.

In the case of rat hepatoma, produced by feeding with butter yellow, it was shown by Weiler that the normal liver stained and fluoresced brightly but the tumor tissue did not.

Further study indicates that this is not necessarily a serologic reaction. The phenomenon can be observed when the globulin is taken from a rabbit that has not been injected with tissue. This places the reaction on a simple physicochemical rather than a serologic plane.

Attempts have been made to apply this method to the naturally occurring neoplasms of man. At first serum from rabbits, which had been injected with homogenates of various human tissues, were employed and a clear distinction between a tumor and its corresponding normal (or even hyperplastic) tissue was obtained. As it became clear that a globulin which was not specifically antigenic was suitable in animals, a simple globulin was employed also for the human tissues. This was found to be thoroughly satisfactory and has been employed with carcinoma of the colon (7), carcinoma of the breast (10), and in leukemia (8, 9).

Some observations on tumors of the skin suggest that in man this kind of phenomenon may not occur. Hiramoto and Pressman have described an epidermoid carcinoma and a melanoma which stain in the same way as normal tissues. This question has been studied and the results obtained are recorded here.

MATERIALS AND METHODS

Preparation of sera. An ammonium sulfate precipitated globulin fraction from the serum of nonimmunized rabbits was, after dialysis, coupled with fluorescein isocyanate (isomer I) by the method of Coons and Kaplan. Excess unconjugated fluorescein derivatives were removed by ethyl acetate extraction as described by Dineen and Ada.

Preparation of tissue sections. Tissue sections were cut from the margins of spontaneously occurring tumors in man and of experimentally induced skin tumors in mice (Fig. 8) after painting with black coal tar (B.P.) 6

days per week for 16 weeks. In each case a small piece of fresh biopsy material, not more than 5 millimeters thick, was snap frozen by dropping into a tube of isopentane, kept at −70 degrees C., in a Dewar flask which contained an ethanol-dry ice mixture. From these tissues unfixed frozen sections were cut at 5 to 7 microns by a method previously described (5). The sections were then dried in a cold room at 0 degrees C. with the aid of a fan for 1 to 2 hours, again immersed in absolute ethanol at −20 degrees C. for 15 minutes and dried in the cold room overnight.

Staining of tissue sections. Staining was carried out at room temperature. Each section was covered with 3 to 4 drops of fluorescein-globulin complex and allowed to stain for 10 minutes. After staining these were washed in 3 changes of buffered saline *p*H 7.3 for 10 minutes when they were ready for examination with a fluorescence microscope.

Microscopy and photography. For microscopy a Leitz fluorescence microscope, fitted with a 10 ampere direct current carbon arc lamp with clockwork feed as a source of light, was used. Between the light source and the condenser were placed two BG12, 4 millimeter filters and a wratten G15 gelatin filter in the ocular. For photography pan F film was used with exposure times of 45 seconds.

The emphasis in this study has been on the comparison of the staining characteristics of the tissues by the fluorescent stain with those of hematoxylin and eosin. As a result the same areas were examined and photographed after using both stains so that the same cells could be compared in the photographs.

RESULTS

In order to assess adequately the fluorescein-globulin staining characteristics of normal skin it was essential to exclude any extrinsic or autofluorescence present independent of the stain. The importance of concentrating only on the specific green fluorescence of fluorescein cannot be overemphasized as naturally occurring green fluorescence is extremely rare while other fluorescence, particularly blue or yellow, is relatively common. In this regard special attention must be paid to the skin because keratin emits a blue-white autofluorescence and elastic tissue a bright yellow one when viewed with ultraviolet light. In the present series a particular effort was made to avoid confusing these with the characteristic green fluorescence which occurs after staining with the fluorescein-globulin complex.

FIG. 1. Normal epidermis. Unfixed frozen section stained with fluorescein-globulin complex showing a bright fluorescence of the epithelial cells. Nuclei do not stain. × 280.

The array of tissues investigated by this method of study is presented in Table I.

The staining characteristics of normal skin were investigated. All the cellular layers of the epidermis have a strong affinity for fluorescein-globulin complexes and fluoresce bright green in ultraviolet light (Fig. 1). All sections examined showed an even distribution of the dye within the cells in which the cytoplasm but not the nucleus fluoresced. As mitotic figures in the basal layers of the epidermis occur frequently it was of interest to note that cells in the process of mitosis fluoresced as brightly as in the surrounding

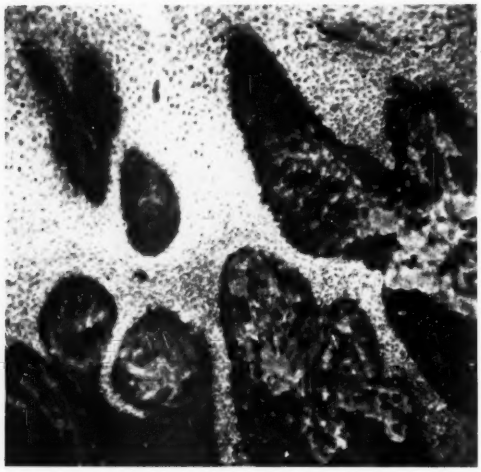

FIG. 2.

FIG. 3.

FIG. 2. Hyperkeratotic wart. Photomicrograph of unfixed frozen section stained with fluorescein-globulin complex showing a bright fluorescence of all epithelial cells. There is some autofluorescence of the papillae. × 180.

FIG. 3. "Irritated" epithelium. Photomicrograph of unfixed frozen section taken from the periphery of a benign ulcer and stained with fluorescein-globulin complex showing that all the epithelial cells fluoresce. × 180.

cells; so that loss of staining is not a function of cell division. This has been shown experimentally in the liver (6).

Several examples of hyperkeratotic warts were investigated. These showed various degrees of irregular downward proliferation of epithelium but without frank invasion. In all cases the epithelium stained and fluoresced as does normal epithelium (Fig. 2).

The series included 12 cases of "irritated" epithelium seen at the edges of benign ulceration. The epithelial hyperplasia closely resembled that of a squamous cell carcinoma with irregular invasion of the dermis. These cases also showed a bright fluorescence of the epithelial cells (Fig. 3) which was indistinguishable from the adjacent normal epithelium.

All of the 6 cases of molluscum pseudocarcinomatosum examined fluoresced brightly. The hyperplastic cells and those which were in the actual process of mitosis fluoresced as uniformly as normal epithelium. No "island of loss" was observed in any of the cases investigated.

One example of an innocent tumor (sudoriferous adenoma) which was well differentiated and sharply demarcated from the surrounding tissue also fluoresced brightly (Fig. 4).

Various examples of squamous cell carcinoma, ranging from the well differentiated type with well developed prickles and many keratin pearls (Fig. 5) to the poorly differentiated type in which keratinization is absent and the squamous cells are completely atypical and devoid of prickles, were investigated. There was complete absence of fluorescence in all the tumor cells examined although there is a sharp change between normal and malignant tissues at the margin of the tumor (Fig. 6). In addition there are areas of decreased staining of healthy epithelial cells in the vicinity of the tumor. The keratin pearls present in the tumor tissue maintain their natural pale blue fluorescence (Fig. 5) in contrast to the nonfluorescing surrounding islands of squamous cells.

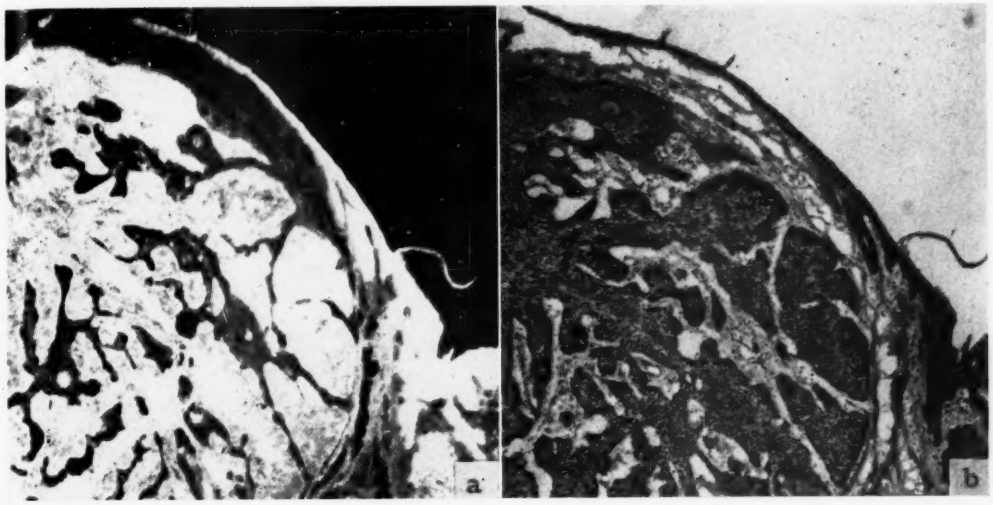

FIG. 4.

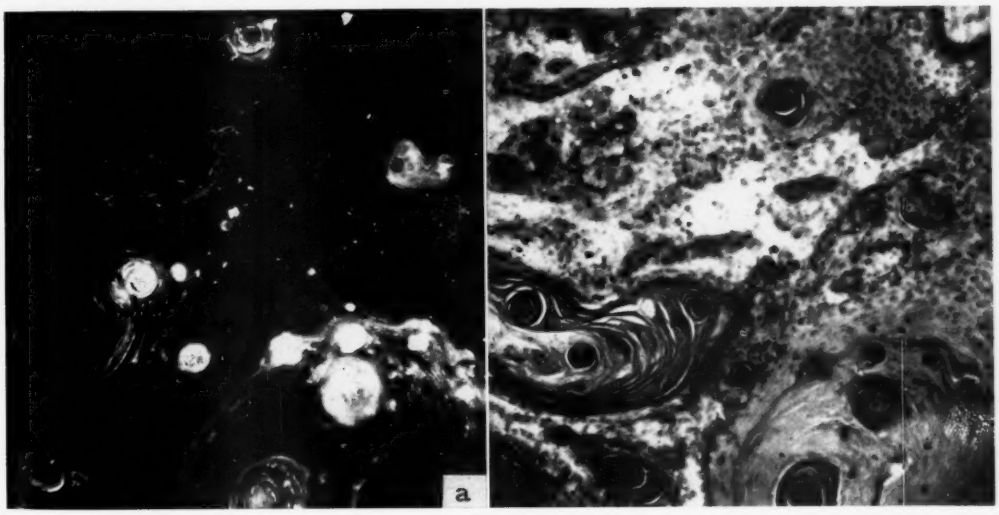

FIG. 5.

FIG. 4. Sudoriferous adenoma. a, Unfixed frozen section stained with fluorescein-globulin complex and showing bright fluorescence of all epithelial cells. b, Same area subsequently fixed in formalin and stained with hematoxylin and eosin for comparison with photomicrograph "a." × 70.

FIG. 5. Squamous cell carcinoma. a, Unfixed frozen section stained with fluorescein-globulin complex. The keratin pearls emit a pale blue autofluorescence (nonspecific) but the surrounding islands of squamous cells do not fluoresce. b, After fixation in formalin and stained with hematoxylin and eosin; compare with "a". × 240.

The basal cell tumors examined also failed to take up the stain (Fig. 7); however, the tissue elements which showed autofluorescence in normal skin likewise showed this property in the tumor.

Examination of sections prepared from the 5 tumors experimentally induced with coal tar which, on routine macroscopic and microscopic examination, were shown to possess the characteristic features of malig-

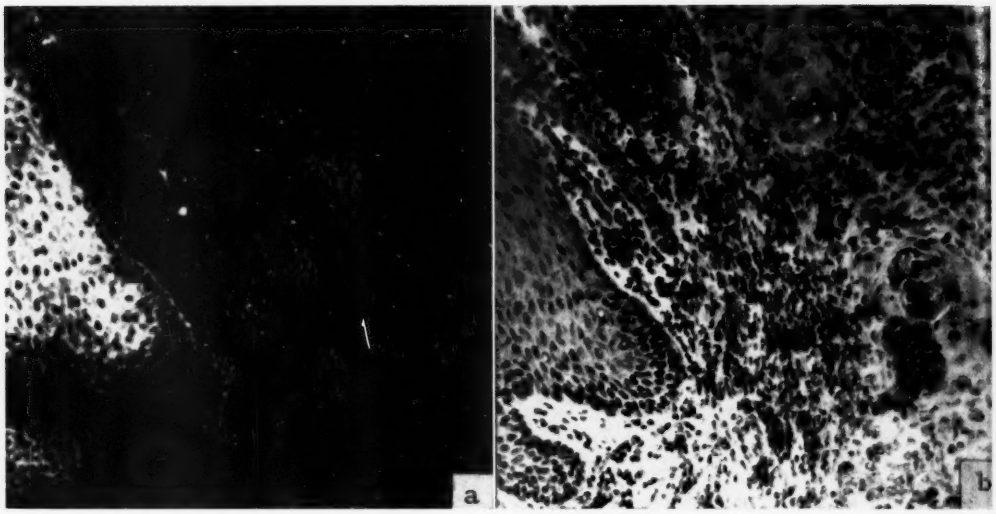

FIG. 6. Margin of carcinoma of lip. a, Unfixed frozen section stained with fluorescein-globulin complex and showing fluorescing epithelium (on left) and a nonfluorescing area (on right). The stratified squamous epithelium (on left) shows nonfluorescing normal cells ("islands of loss"). b, Same area after fixation in formalin for comparison. × 220.

nancy (Figs. 8 and 9) gave analogous results in that the malignant cells had no affinity for the fluorescent stain (Fig. 10). In common with the spontaneously occurring tumors examined, any structures in these tumors which normally gave autofluorescence again showed this feature. On the other hand, the papillomas which occurred in the early stages of carcinogen application showed normal staining just as do other hyperplastic states. They also showed groups of histologically innocent cells which failed to fluoresce.

DISCUSSION

The histologic method, described in this article, which distinguishes between a neoplastic and a nonneoplastic cell has now been employed in a sufficiently large number of cases of different kinds of tissues and tumors to demonstrate, beyond all reasonable doubt, that it applies consistently to both the experimentally induced tumors of animals and naturally occurring neoplasms in both animals and man.

There are, at present, differences of opinion as to whether it is some kind of specific serologic phenomenon (particularly in some of the experimentally produced growths) or a nonspecific physicochemical reaction. The evidence obtained in this laboratory, however, indicates that the second view is correct. This part of the problem is being dealt with in another article (4) but, irrespective of any interpretation placed on the results, the observation of a difference between neoplastic and nonneoplastic tissue is well defined and, in a considerable series of cases, has been consistently reproduced.

Observations have been made on tumors occurring in various organs. Results may be obtained from cases found at postmortem examination but, in general, attention has been directed especially to surgically removed specimens. These include, in addition to those already recorded, tumors of the lung, stomach, and kidney among others. Incidentally, some naturally occurring tumors in mice and rats have also been studied.

It might have been expected that skin tumors would have been studied first. Indeed, some were examined at an early stage of the investigation but several technical

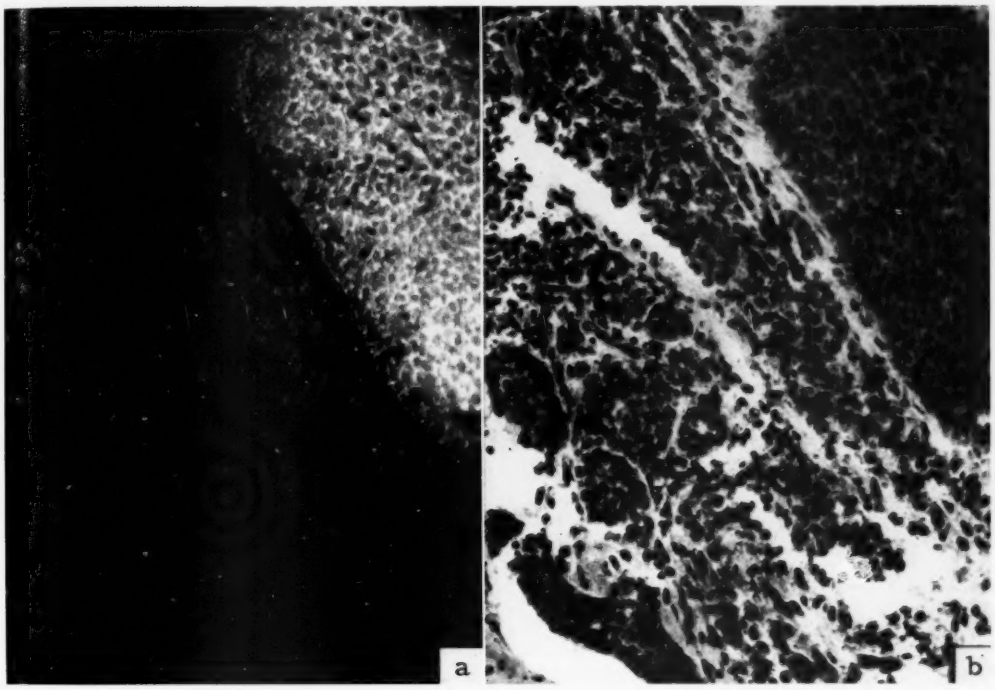

FIG. 7. Basal cell carcinoma. a, Unfixed frozen section with fluorescein-globulin complex and showing the epithelial cells of a rete peg fluorescing (on top right). b, Same area after fixation with formalin and stained with haematoxylin and eosin for comparison with "a" and showing masses and groups of epithelial cells in the tumor area. × 280.

difficulties were encountered and apparently contradictory results obtained. These began to be reconciled at an early stage but they demanded a more extensive survey of material than was necessary for the early steps of the study of other tumors; the presentation of results has, therefore, followed rather than preceded that of other tumor types.

The problems arose first from the wide range of structures—from well organized basal cell to anaplastic epidermoid tumors—which are all similar in that they are neoplasms, and secondly from "irritated" epithelium and molluscum sebaceum (pseudocarcinomatosum) which despite morphologic similarities to carcinoma, are very different in kind and behavior. Further complications arise among the hyperplasias of the epidermis, some of which are benign but others precancerous.

In all specimens the epidermis and cells of the adnexa stained well and fluoresced brightly in a green color (with fluorescein). Other dyes have been used and are discussed elsewhere (4). When there was downgrowth of epithelium in the form of "irritated" epithelium (Fig. 3), this tissue stained as well as did the adjacent normal epithelium. This observation conformed with those made on the hyperplastic tissue of the regenerating liver (6).

Specimens of warts of various kinds showed well developed fluorescence of the epithelium. Here, especially, though also in other conditions, keratin fluoresced a bluish-white color which had to be distinguished from that of the stained tissue; examination of tissue before staining helped to make the distinction clear.

In the experimental skin tumors both

FIG. 8.

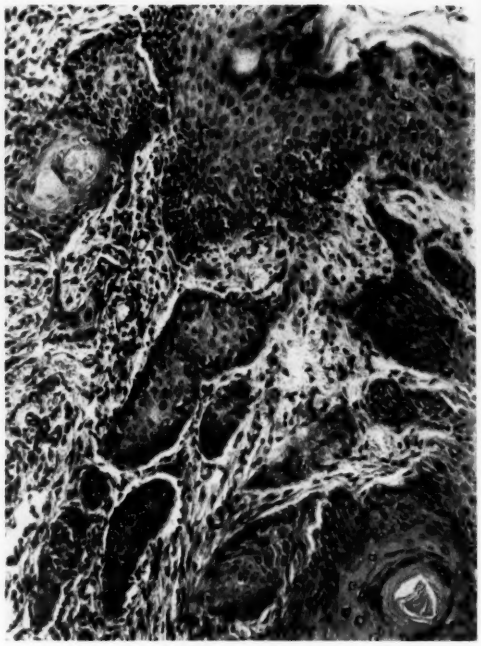

FIG. 9.

FIG. 8. Strain A mouse showing a large malignant tumor and several small papillomas. These were induced with black coal tar (B.P.). × 0.85.

FIG. 9. Paraffin section from the largest tumor of the mouse shown in Figure 8 demonstrating the histologic structure of the growth. There are islands of epithelial cells showing squamous differentiation and formation of cell nests. × 200.

innocent and malignant proliferations were found. In the early stages the growths were papillomas and these stained in the same way as did normal tissue or simple proliferations. Examples showing the transformation to the malignant state have also been observed and studied and they have shown the characteristic loss of staining.

Some of the hyperplasias in man, especially those known as molluscum sebaceum or pseudocarcinomatosum, presented some difficulties at first. This condition closely resembles a squamous cell carcinoma and, indeed, was for long so diagnosed. All of those examined so far have stained and fluoresced as normal tissues but since some have been shown clinically to be presumably truly neoplastic, this may not continue to be uniformly true. It is clear that continued scrutiny of these growths is necessary. The present interpretation of this study is that tumors diagnosed as molluscum sebaceum are in fact hyperplasias (as is now generally thought) but others so diagnosed but differing in their clinical course are actually true neoplasms. It is important here to remember that the modern view of the nonneoplastic nature of these growths is indeed modern. One encounters mistakes in prognosis in this group and it is apparent that all of its peculiarities have not yet been thoroughly elucidated. The observations made here conform with some clinical observations made on these growths. Examples of innocent tumors are infrequent but the observation of one which fluoresced brightly is of special significance.

All the forms of indubitable malignant skin neoplasms in this series failed to stain. This was particularly striking in some of the basal cell tumors. In many of the growths examined, it was not possible to make extensive studies, since material was obtained in some by punch biopsy but the amount of tissue in these cases was always sufficient to make observation of part of a small tumor practicable.

In the case of epidermoid growths, where

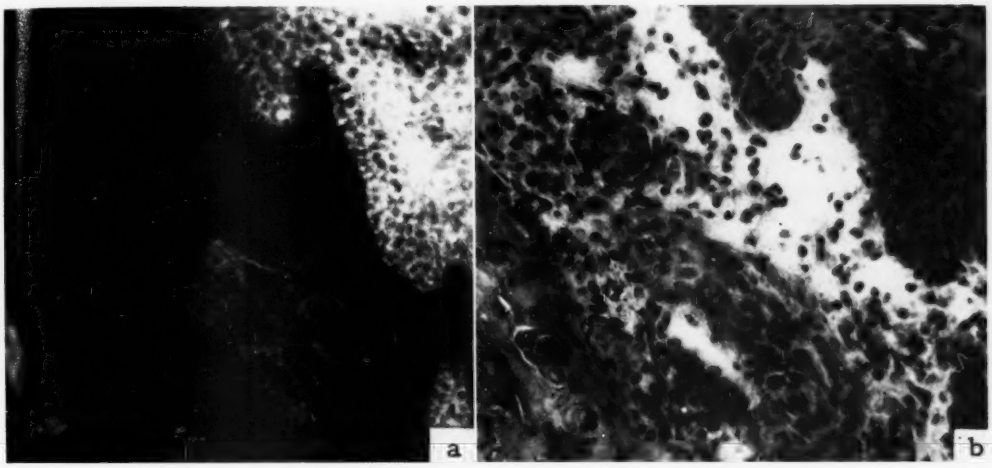

FIG. 10. Margin of skin tumor from Figure 8. a, Unfixed frozen section stained with fluorescein-globulin complex and showing fluorescence of stratified squamous epithelium (on top right). There is a slight autofluorescence of elastic fibrils. b, Same area after fixation in formalin and stained with hematoxylin and eosin to show the structure of the nonfluorescing area. × 280.

there was considerable differentiation to keratin (Fig. 5), this sometimes gave an appearance which was, at first, confusing. The anomaly was disentangled when it was appreciated that the fluorescence of the keratin was an autofluorescence of a color different from that produced by fluorescein staining. The value of the use of globulin-rhodamine in such cases is apparent.

Intraepithelial tumors gave a characteristic appearance of round defects (of cellular size) in the fluorescing epithelium, due to the presence of nonfluorescing cells. It was necessary to distinguish these from areas of loss of fluorescence found in zones in which a precancerous condition was present. In general, the difference, of individual cells as opposed to small areas of loss of staining, was characteristic.

The areas of loss of staining are well known in the liver of rats fed with carcinogenic dyes; these have been interpreted as being precancerous in nature. Similar, and presumably comparable, areas have been observed in polyps of the colon in multiple polyposis and in the breast; these have been regarded as having a similar significance. In the skin, these areas have certainly been found to correspond with areas which were regarded, on clinical grounds, to be precancerous. Further study is necessary, but it would appear that this method may prove to be of value in cases in which the nature of the condition is in doubt.

There are still considerable technical difficulties in the use of this method. The preparation of the globulinfluorescein stain is a process which is intricate rather than difficult and the material must be kept at a temperature below freezing point. Freezing and thawing soon vitiate this material as well as the tissue. The various absorptions require careful attention. Section cutting (in a deep freeze) is a technique rather different from that normally applied and the necessity for not allowing the tissue to come to melting point demands modifications of normal procedures (5). None of these nor, indeed, all of them together presents insuperable difficulties but, until simplification of technique has been achieved, they make the method a more exacting one than usual.

Interpretation of appearances is complicated by the occurrence of a natural fluorescence (autofluorescence) in some components as opposed to the green fluorescence

due to the stain. This autofluorescence is usually of a different color and is well seen in the elastic tissue of the walls of blood vessels (where it is yellow) and in keratin (where it is bluish-white).

The importance of this method of study is considerable from the point of view of the laboratory worker. It has a clear import in the nature of the difference between the neoplastic cell and its normal counterpart. The indication that the stain is effective because of certain physicochemical reactions between proteins (the basic soluble proteins of the cytoplasm and the γ-globulins of the serum) opens up many possibilities for further basic study.

Its value in the elucidation of the nature of neoplastic and potentially neoplastic conditions needs no emphasis and, as a corollary of this, its use (or that of some related method) as a routine method of investigation is probable in the near future, as soon as the technique is suitably simplified.

SUMMARY

A study of epidermoid tumors of the skin has been made using a staining technique which distinguishes between normal and malignant cells.

Employing a complex globulin-fluorescence stain, normal tissues stain and fluoresce in ultraviolet light but malignant tumors do not.

These observations have been developed from those made in cancer experimental work in which normal rat liver stained with rabbit globulin-fluorescein but hepatomas (following feeding with butter yellow) did not. The method has been applied to naturally occurring tumors in animals and man and the same distinction has been observed regularly.

The method began to be employed as an antigen-antibody reaction using "organ specific" antisera. However, it has been shown that a simple globulin fraction from any animal gives a similar result and this provides a desirable simplification of the method. It also has far-reaching effects on our explanations of the phenomenon.

REFERENCES

1. Coons, A. H., and Kaplan, M. H. Localization of antigen in tissue cells—II, improvements in a method for the detection of antigen by means of fluorescent antibody. J. Exp. M., 1950, 91: 1–13.
2. Dineen, J. K., and Ada, G. L. The rapid extraction of free fluorescein derivatives from fluorescein isocyanate-globulin conjugates with ethyl acetate. Nature, Lond., 1957, 180: 1284.
3. Hiramoto, R., and Pressman, D. Immunochemical staining properties of the human skin and some related tumors. Proc. Am. Ass. Cancer Res., 1957, 2: 213.
4. King, E. S. J., Hughes, P. E., and Louis, C. J. The species non-specificity of globulins in the globulin-fluorescein staining of tissues. Brit. J. Cancer, 1958, in press.
5. Louis, C. J. Cutting unfixed frozen sections for fluorescence antibody studies. Stain Tech., 1957, 32: 279–282.
6. Idem. Histochemical differences between regenerating and neoplastic rat liver. Austral. Ann. M., 1957, 6: 277–281.
7. Idem. A study of carcinoma of the colon using an histochemical technique. Austral. N. Zealand J. Surg., 1957, 27: 146–154.
8. Idem. The nature of leuchaemia—I, a histochemical study of the leuchaemic cell in man. Austral. Ann. M., 1957, 6: 300–310.
9. Idem. The nature of leuchaemia—II, a histochemical study of the leuchaemic cell in animals. Austral. Ann. M., 1958, in press.
10. Idem. Tumours of the breast; a study employing an histochemical technique. Brit. J. Surg., 1958, in press.
11. Miller, E. C., and Miller, J. A. The presence and significance of bound aminoazo dyes in the livers of rats fed p-dimethylaminoazobenzene. Cancer Res., 1947, 7: 468–480.
12. Sorof, S., and Cohen, P. P. Electrophoretic and ultracentrifugal studies on the soluble proteins of various tumors and of livers from rats which were fed 4-dimethylaminoazobenzene. Cancer Res., 1951, 11: 376–387.
13. Weiler, E. Die Aenduring der serologischen Spezifitaet von Leberzellen der ratte waehrend der Cancerogenese durch p-Dimethylaminoazobenzol. Zschr. Naturforsch., 1956, 11b: 31–38.

THE DETERMINATION OF FRACTURE HEALING BY MEASUREMENT OF SOUND VELOCITY ACROSS THE FRACTURE SITE

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Hines, Illinois

THE EVALUATION of fracture healing is dependent upon roentgenographic and physical examination of the involved bone.

Such methods are subject to error. The x-ray examination does not always indicate the true state of healing, the amount of apparent callus often correlating poorly with an accurate estimate of bony union. Subjective physical examination is often equivocal, and the final assessment of union ultimately becomes a matter of clinical judgment.

The advantages of a more objective method of analyzing the degree of healing of a fracture are at once apparent. If the state of union could be determined with greater accuracy, delayed union and nonunion might be diagnosed and treated earlier. In fractures of the lower extremity, the risk of premature ambulation could be avoided. Finally, a method of critically evaluating a fracture at any stage of healing would not only aid in reducing morbidity in fracture cases but should be of value to both clinical and laboratory investigation in the field of traumatic pathology.

This article is a preliminary report on an investigation proposed by one of us (G.T.A.) to provide such a method through the measurement of sound velocity across a fracture site compared to that of the opposite normal extremity (1).

BACKGROUND

Measurement of the velocity of sound through a medium has long been used to test the quality of materials. Velocity is a function of both the elastic modulus and the density, the former depending upon the strength of the material. Velocity can be derived from the formula:

$$V = (E/D)^{1/2}$$

Where: E = Young's modulus
D = density

It has been demonstrated by Whitehurst and Long, Kurtz, and Sandenaw that velocity of sound measurements can be used to determine the internal integrity of cement forms under conditions of compression, flexure, and aging.

Sound transmission studies and sonar ranging techniques have been used in efforts to locate and map areas of malignancy in the brain and other tissues. Sound velocity measurements have been made in bone but have had little application in clinical situations.

METHOD

The techniques employed in this study are similar to those used in the reports cited (2, 4). The method consisted of sending a short duration, sonic pulse through a leg by means of a transmitting transducer and measuring the time for this pulse to reach a receiving transducer. The sound pulse was obtained by applying a rapidly varying potential from a thyratron tube to a piezoelectric crystal. A small, rubber pillow (filled with oil) was mounted on the crystal and the vibrations were thereby transmitted from the crystal to the leg. The received signals were similarly converted into an electrical

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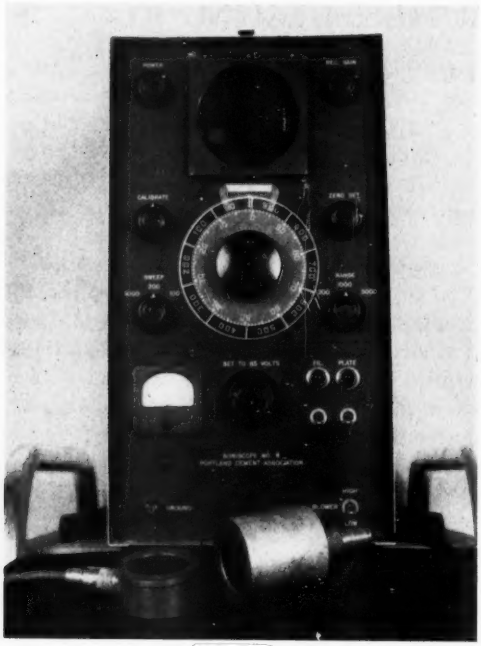

FIG. 1.

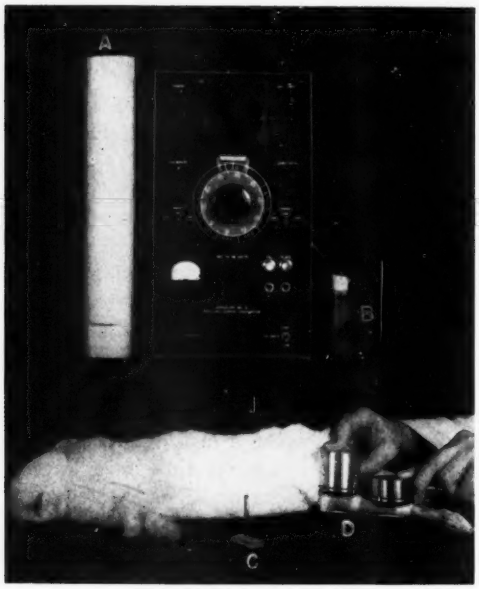

FIG. 2.

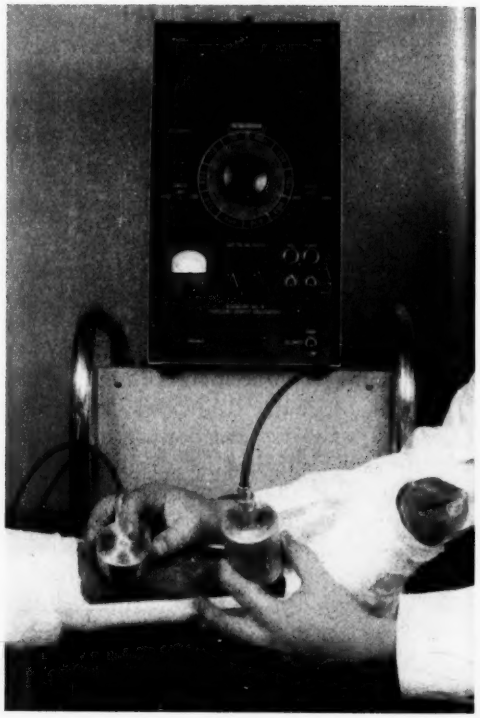

FIG. 3.

FIG. 1. The soniscope.

FIG. 2. Soniscope in use on rabbit. The animal is anesthetized. Note: *A*, wood block for standardizing apparatus; *B*, glycerine used for adequate transducer skin contact; *C*, spacer for measuring transducer separation; *D*, method of splinting fractured tibia.

FIG. 3. Fractured limb examined through a cast window with soniscope. It is unnecessary to manipulate or otherwise disturb the fracture site with this technique.

signal which was amplified and applied to the upper trace of a double beam oscilloscope. The lower beam was used as a time base marker to measure the elapsed time between the transmitted and received pulse. This time interval was read from a 10 turn potentiometer dial calibrated in microseconds (Fig. 1).

All readings were taken with transmitter and receiver applied to the skin. Since skin, subcutaneous tissue, and periosteum were interposed between the instrument and bone, any velocities or changes in velocities must be termed apparent. Experimentation with

animals and cadaver material revealed that such interposed material introduced only a slight error.

Observations of sound velocity were made on both intact and fractured tibias. The tibia was used exclusively because it is frequently injured, often the site of nonunion, and easily tested with these techniques.

A series of litter-matched rabbits were examined as follows: Control readings of both legs were taken with the transmitter placed over the upper and the receiver over the lower one-third of the subcutaneous border of the tibia and separated by ½ inch. The right leg was then surgically prepared and, under aseptic conditions and intravenous nembutal anesthesia, an osteotomy of the middle one-third of the tibia was performed. In 4 instances, the use of a bone forceps resulted in comminution. Otherwise, a Gigli saw produced uniformly noncomminuted transverse fractures. The fractured limb was immobilized on a tongue-blade splint, and sound velocity readings were taken across the fracture site and compared to those of the contralateral normal extremity daily until the fractured tibia was clinically solid (Fig. 2). The same relative transducer position and the same transducer separation (½ inch) was employed in all readings on both intact and fractured legs. In testing fractured legs, the fracture site was always between the two transducers.

Sound velocity examinations were also made on human tibial fractures at various stages during healing (Fig. 3). The extremity to be examined was placed in a comfortable position on the bed or a cushioned support. Fractured limbs were examined through a cast window or with a posterior plaster shell in place. Measurements were taken on the normal limb by using the tip of the medial malleolus as a reference point and placing the transmitter 5 centimeters cephalad. Readings were then taken with the receiver placed proximal to this at 5 centimeter intervals over the flat surface of the bone. The same procedure was then performed on the fractured limb, the fracture site always lying between the two transducers.

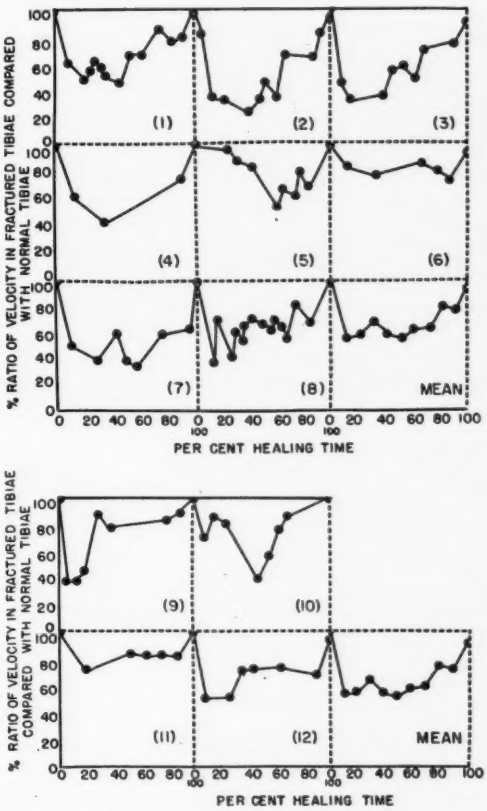

FIG. 4. Sound velocity change correlated with per cent healing time in fractures of rabbit tibias (12).

Calculations of velocity were made from the formula already expressed. For purposes of comparison in normal and fractured limbs it appeared sufficient to compare the elapsed times for similar paths rather than to calculate the velocities.

RESULTS

Of 16 rabbits examined, 12 fractured tibias healed without complication. Although overriding was present in all fractures and no attempt was made to prevent weight bearing, clinical solidity, judged by inability to elicit motion at the fracture site, was present in from 9 to 29 days. Though

FIG. 5.

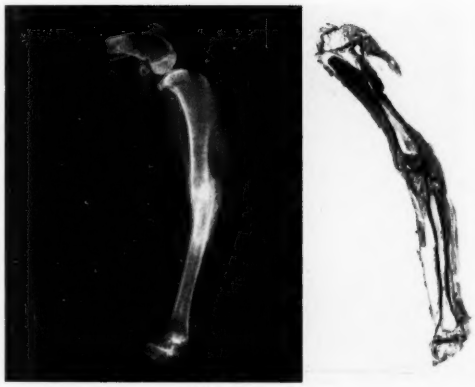

FIG. 7.

FIG. 6.

FIG. 8. FIG. 9.

FIG. 5. Rabbit tibia 7 days postfracture. No calcification at fracture site indicated on x-ray film. Microsection shows organizing hematoma with invasion of granulation tissue, fibrosis, and some cartilage formation. Sound velocity 52 per cent of normal.

FIG. 6. Rabbit tibia 14 days postfracture. X-ray film reveals calcification occurring at fracture site. Microsection shows chondrification with calcium deposition and scattered areas of ossification as union proceeds. Sound velocity 86.3 per cent of normal.

FIG. 7. Rabbit tibia 25 days postfracture. Roentgenographically, clinically, and histologically united. Intercortical ossification has occurred. Sound velocity 100 per cent of normal.

FIGS. 8 and 9. Healed tibial fractures in rabbits. Intact tibias included for comparison. Though these fractures healed with different angulation, sound velocity was identical across the fracture sites and equal to that of normal bone at the time of clinical union.

sound velocity in the fractured legs was reduced immediately after surgery and during healing, a normal velocity (as compared to that of the opposite, intact "control" extremity) was always obtained at the time of clinical union (Fig. 4). Microscopic sections of fracture sites at various stages of healing, as well as x-ray films of these tibias when each leg was removed, were taken in an effort to provide historadiographic correlation of the state of fracture union and the sound velocity reading (Figs. 5, 6, and 7). Sound velocity was identical across healed fractures and normal bone whether measured in vivo or on the isolated bone after sacrificing the animal (Figs. 8 and 9).

One animal developed osteomyelitis at the fracture site. This delayed but did not prevent eventual union, the sound velocity returning to normal when the bone was

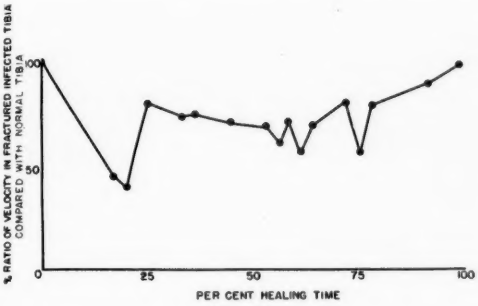

FIG. 10.

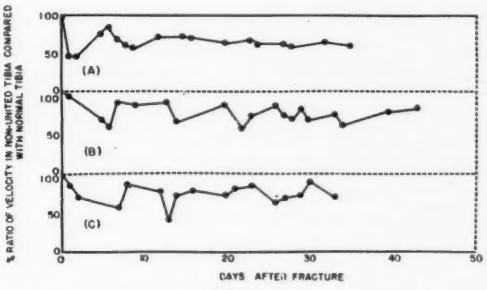

FIG. 11.

FIG. 10. Sound velocity change correlated with per cent healing time in infected fracture of rabbit tibia.

FIG. 11. Sound velocity change correlated with elapsed time after fracture in nonunions of rabbit tibias (3).

clinically solid even though minimal purulent drainage was present (Fig. 10). Three fractures eventuated in nonunion. In each of these, gross motion was present at the site of fracture and sound velocity did not return to normal. It remained between 50 and 80 per cent of normal for as long as 14 days after the time when union was obtained in the slowest of the healing fractures (Fig. 11).

A series of 26 patients with tibial fractures at various stages of healing as well as groups of normal and osteoporotic tibias was also examined.[1]

In a group of 20 normals, the average velocity recorded over a 15 centimeter path was 3,481 meters per second with a range of 3,260 to 3,572 meters per second. The effect of osteoporosis on sound velocity readings was determined by examining a series of 11 paraplegic limbs, sound velocity readings of which were noted to overlap our range of normal. Repeat examination of any limb on different occasions showed a variation of ± 5 per cent from the mean.

In studying 26 patients with tibial fractures, sound velocity was slowed from 4 to 40 per cent of normal. The velocity of sound appeared to be related to the degree of fracture union. We were not afforded the opportunity to examine any one patient serially from injury until complete healing. We did observe, however, that human fractures at various healing times had sound velocity readings below those of the normal contralateral tibia, that fractures when united and bearing weight had normal sound velocity, and that established nonunions showed below normal readings which did not significantly change on several examinations at biweekly intervals. Despite these observations, direct application of the animal data to human fracture evaluation must await further study.

[1]No fractures under treatment with metal appliances were included in the study. With the exception of 3 patients examined at another hospital, all readings were made on patients or employees of the Veterans Administration Hospital, Hines, Illinois.

CONCLUSIONS

The work of previous investigators, notably Urist and Johnson, has clarified the histologic sequence which occurs during fracture healing. Our data suggest correlation between alterations of sound velocity and this sequence.

Shortly after injury, the fracture gap is filled with hematoma, relatively homogeneous and able to conduct sound almost as well as normal bone. At this time, sound velocity across the fracture site is but slightly reduced. As union progresses, this hematoma organizes, is invaded by granulation tissue, and gradually assumes the features of procallus. Apparently this stroma is more resistant to the passage of sound, and velocity across the fracture site drops concurrent

with its formation. As fibrocartilaginous substitution occurs in the now maturing callus, the sound wave is further impeded (this may be related to disorientation of cartilage trabeculae from the longitudinal axis of the bone[2]); and it is not until the process of intercortical ossification between the fracture fragments is initiated that the sound velocity curve begins to ascend toward normal.

SUMMARY

1. A method of determining the state of healing in fractures by serial sound velocity measurement across the fracture site has been described.

2. In a series of 16 tibial fractures in rabbits, a pattern of sound velocity change which seemed to parallel the progress of fracture union was noted.

3. Examination of 26 fractured human tibias indicates that sound velocity is decreased across nonhealed fracture sites. These preliminary observations warrant further studies.

[2]This type of phenomenon has been observed in the variation of sound velocity along the fiber of wood grain as compared to the velocity across the grain.

REFERENCES

1. Anast, G. T., Fields, T., and Siegel, I. M. An ultrasonic technique for the evaluation of bone fractures. Read before the International Conference of Ultrasonics in Medicine at Los Angeles, California, September 6, 1957.
2. Long, G. B., Kurtz, H. J., and Sandenaw, T. A. A report upon an instrument and a technique for field determinations of the modulus of elasticity and flexural strength of concrete. J. Am. Con. Inst., 1945, 41: 217.
3. Urist, M. R., and Johnson, R. W. Calcification and ossification. J. Bone Surg., 1943, 25: 375.
4. Whitehurst, E. A. Soniscope tests concrete structures. J. Am. Con. Inst., 1951, 47: 433.

A NEW APPROACH TO THE PROBLEM OF URINARY RETENTION FOLLOWING ABDOMINOPERINEAL RESECTION FOR CARCINOMA OF THE RECTUM

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A STUDY has been made of the problem of urinary retention following abdominoperineal resection for carcinoma of the rectum. In the present article a new approach to the problem is proposed as well as more radical surgery when carcinoma of the rectum overlies or is attached to the prostate or seminal vesicles.

The most common urologic complications following abdominoperineal resection for carcinoma of the rectum are inability to void and residual urine. There are two principal types of postoperative vesical dysfunction. The first is primarily neurogenic and is produced by wide pelvic dissection with associated severance and trauma to bladder innervation. This type is relatively uncommon, occurring in less than 5 per cent of the patients. The second and most common vesical dysfunction results from a combination of factors: postoperative distention, benign prostatic hypertrophy, trauma to local tissues with associated pericystitis, trauma to nerves, and prolapse of the bladder into the pelvis. Prolapse of the bladder accentuates the angulation of the prostatic urethra to the bladder neck and may form an obstructing median bar. Preoperative, asymptomatic, mild vesical neck obstruction (benign prostatic hyperplasia, median bar or vesical neck contracture) may become very significant when associated with the operative trauma to nerves, tissues, and pelvic prolapse of the bladder. The postoperative problems due to neurogenic vesical dysfunction have been studied by Marshall, Campbell, Flint, Ewert (4) and Emmett and Bacon and their associates. Benign prostatic hypertrophy is the immediate concern of this study.

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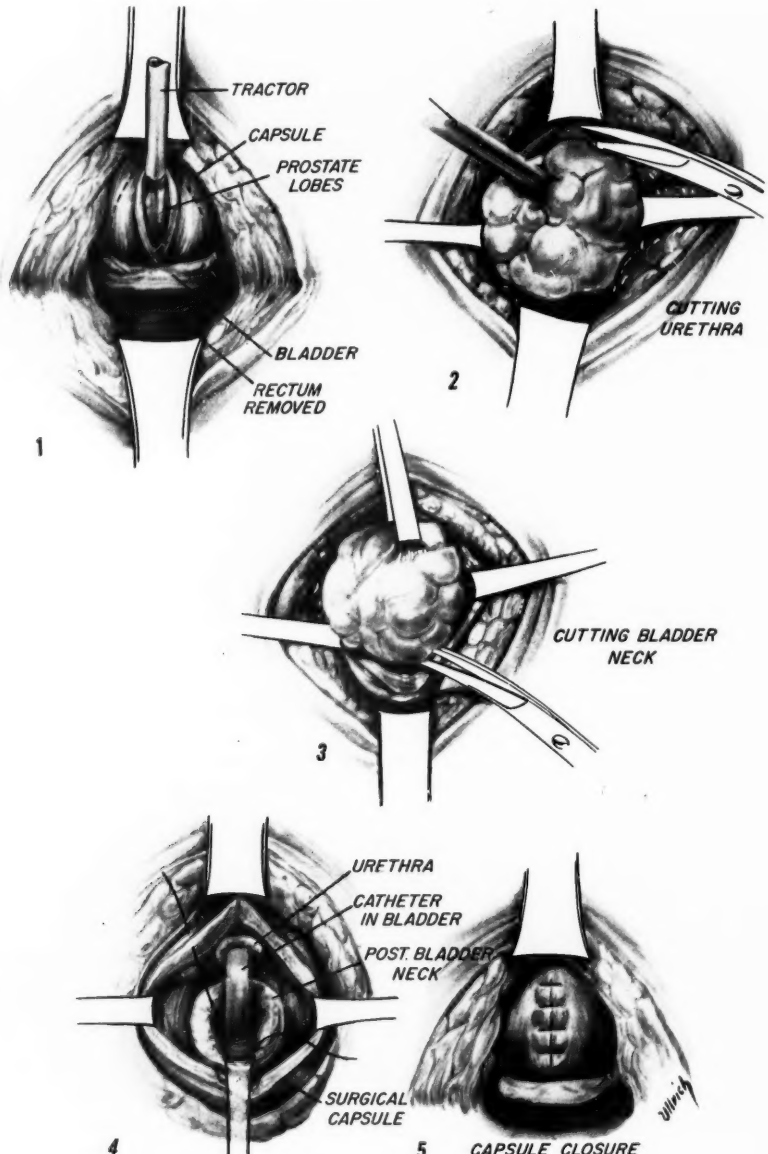
THE INCIDENCE AND TREATMENT OF POSTOPERATIVE URINARY RETENTION FOLLOWING ABDOMINOPERINEAL RESECTION

The records of 62 males who had abdominoperineal resection for carcinoma of the rectum have been reviewed. All except 3 were men over 50 years of age. Eighteen per cent of the patients studied had a prostatectomy. One was performed prior to, the remaining following, abdominoperineal resection. In this group one had a perineal prostatectomy, the remainder transurethral resections. The necessity for prostatectomy was realized preoperatively in only 1 case. All others had several episodes of postoperative acute urinary retention before prostatectomy was decided upon. One patient for example had 3 episodes of urinary retention while recovering from abdominoperineal resection but before discharge was "voiding well." He was not catheterized for residual urine and the symptoms of prostatism increased markedly over a 2 year period. At the end of this time urinary obstruction was relieved by prostatectomy.

How can one anticipate difficulty or predict the need for prostatectomy preoperatively? The answer is simple—systematic urologic evaluation. The urologic history with reference to frequency, nocturia, hesitancy, and decrease in size and force of



FIGS. 1 to 5. Technique of simple prostatectomy following abdominoperineal resection.

FIG. 1. Vertical incision in the prostate with the straight Young tractor in the bladder.

FIG. 2. Cutting the distal urethra within the prostatic capsule and at the apex of the prostate.

FIG. 3. Cutting the bladder neck and removal of the adenoma.

FIG. 4. Suture of the posterior bladder neck to the prostatic capsule.

FIG. 5. Closure of the prostatic capsule.

the urinary stream is essential. A careful rectal examination with attention to the size of the prostate, as well as to the rectal tumor must be performed. A record should be available of residual urine, cystoscopy, panendoscopy, and intravenous urogram. It seems needless to record these basic procedures; however, in this series, 66 per cent or 40 patients had a history, rectal findings, or both, indicating prostatic obstruction. Only 1 of these patients had preoperative catheterization for residual urine. Only 43 per cent or 16 patients had preoperative cystoscopy and only a fraction of this number had panendoscopy. If these cases had been evaluated as outlined, planned prostatectomy would have been performed in more cases and thus postoperative urinary complications would have been avoided.

A few patients will have postoperative vesical complications, in spite of good preoperative evaluation. In some, primary neurogenic dysfunction will develop and in a small number bladder difficulties will develop because of presumed insignificant vesical neck obstruction. In this group the "insignificant obstruction" associated with operative trauma to nerve tissue and pelvic prolapse of bladder becomes significant.

The urologic follow-up is too often neglected or inadequate; notes in the record state: "patient voiding satisfactorily." Postoperative residual urine was obtained in only 6 per cent of the patients. Several patients had residual urine of 150 cubic centimeters or more and were discharged without further evaluation because they appeared to be voiding satisfactorily. The fact that patients may void satisfactorily and yet retain significant residual urine is well recognized by urologists. Residual urine signifies stasis, infection, and portends renal damage. Sixty-six per cent of the patients had no apparent postoperative difficulties and remained well. The records, however, were inadequate and in many of the patients the presence or absence of residual urine or urinary symptoms was not noted. It was assumed that no news was good news.

Thirty-four per cent or 24 of the patients had postoperative urinary complications. What has become of these patients? Fifty-three per cent of these required transurethral resection of the prostate and 47 per cent, or 10, had either moderate to severe urinary symptoms or significant residual urine (over 75 c.c.). This latter group of patients all became asymptomatic within a year. It was not possible to determine the incidence of primary neurogenic vesical dysfunction because of inadequate records. How were these patients treated? All had perineal or transurethral prostatectomy without subsequent complications. However, they were subjected to an additional operative procedure, carrying with it the increased morbidity of a second anesthesia and an additional 1 to 2 hours of surgery. All but 3 of the patients required one or more transfusions during the prostatectomy. For men in this age group convalescing from an abdominoperineal resection, the stress of a second operation is significant. The hospital stay was increased 7 to 19 days, an additional heavy financial burden. These facts simply serve to emphasize that a new approach to the problem is warranted.

SIMPLE PROSTATECTOMY COMBINED WITH ABDOMINOPERINEAL RESECTION

What then is a more satisfactory solution? We believe that patients with a history and diagnostic evidence of prostatic obstruction should have perineal enucleation of the prostatic adenoma at the time of combined resection. Such a procedure adds only 15 to 20 minutes operative time, and does not significantly increase morbidity. This treatment has been successfully accomplished in several instances at the Massachusetts General Hospital. A brief summary of a patient recently treated in this manner will suffice.

E. B. H., an 84 year old white male, was admitted to the Massachusetts General Hospital because of indigestion and "bleeding hemorrhoids." The system review indicated that he had prostatic obstruction evidenced by nocturia, frequency, and dysuria. His past history was long and complicated; he had a

chronic duodenal ulcer of 30 years' duration with 1 episode of melena, coronary artery disease, and a known abdominal aneurysm for 1 year. Physical examination revealed normal blood pressure, pulse, and respirations. He was an alert gentleman in no distress. The liver was 1 fingerbreadth below the costal margin. A large, pulsatile abdominal mass was present. On rectal examination there was a large fungating carcinoma on the posterior rectal wall and an estimated 75 gram prostate. The hemoglobin was 14 grams. The urine showed 3 red cells and an occasional white cell per high powered field. Urine albumin was 1+; urine sugar was negative. Blood nonprotein nitrogen was 28. Cystoscopy and panendoscopy confirmed the presence of an obstructing prostate. The intravenous urogram was normal. Electrocardiograms showed auricular fibrillation. Because of the patient's age and other complicating factors, the operation was staged. Colostomy was performed and, following a 3 weeks' convalescence, perineal excision of the rectum and simple perineal prostatectomy were carried out. The prostatic capsules and perineal wounds were closed primarily and a Foley catheter was left in the bladder. The patient made an uneventful convalescence, and the catheter was removed on the tenth postoperative day. The patient voided with good control and did not have significant residual urine. The perineal wound healed per primam, and he was discharged on the twenty-first postoperative day. He now has good urinary control, is well, and has no evidence of carcinoma.

TECHNIQUE OF SIMPLE PROSTATECTOMY

Following removal of the rectum, the posterior prostatic capsule is well exposed. A metal sound is first inserted into the urethra. By this means the prostate is levered into the wound and is stabilized. A vertical or inverted V incision is made through the posterior capsule into the urethra (Fig. 1). A vertical incision is preferred because of the ease of closure. The metal sound is removed and a straight Lowsley tractor (Fig. 6) inserted through the prostatotomy into the bladder. With the tractor in the bladder, the prostate may be stabilized and moved as desired during the adenomectomy. A plane of cleavage between the adenoma and capsule is established with the scissors (see Fig. 2) and enucleation begun. When the adenoma has been freed from the capsule, the urethra inside the capsule and at the apex of the prostate is severed with the scissors (Fig. 2). Care must be exercised to cut the urethra close to the adenoma thereby avoiding possible trauma to the external urethral sphincter.

After severance of the urethra the adenoma is now attached only at the vesical neck. The tractor is removed and a double hook placed on the apex of the adenoma. With traction on the adenoma the vesical neck can be seen and easily severed (Fig. 3).

Following enucleation a small wedge of tissue should be removed from the posterior bladder neck to prevent subsequent contraction of the bladder neck. Bleeding is usually minimal and can easily be seen and controlled by electrocoagulation or suture. A No. 22 Foley catheter with a 30 cubic centimeter bag is inserted into the bladder. The posterior bladder neck is sutured to the floor of the distal prostatic capsule (Fig. 4). Two sutures are usually adequate. This step serves to reinforce the area and allow more rapid epithelialization. A watertight closure of the prostatotomy is accomplished with interrupted chromic catgut sutures (Fig. 5). The perineal wound is drained in the usual fashion. The urethral catheter may be removed on the tenth postoperative day.

LOCAL INVASION OF THE PROSTATE AND SEMINAL VESICLES BY RECTAL CARCINOMA AND PROPOSED THERAPY

The subject of abdominoperineal resection combined with total prostatectomy and seminal vesiculectomy for rectal lesions near the prostate is an interesting one. It is often stated that Denonvillier's fascia is an effective barrier against direct extension of rectal carcinoma to the prostate and seminal vesicles. This is not always true, since prostatic carcinoma may invade the rectum and rectal carcinoma may invade the prostate, seminal vesicles, and bladder. Oppenheimer analyzed 2 groups of patients with carcinoma of the rectum. The first group was operable and treated by a combined resection. Subsequently, "at least" 10 per cent developed carcinomatous involvement of

the bladder, prostate, and/or seminal vesicles. The next group was found to be inoperable; 50 per cent of these patients had involvement of the prostate, bladder, and/or seminal vesicles at postmortem examination. Kickham reviewed a large number of autopsies of patients with rectal carcinoma. This series of patients had both operable and inoperable disease. Thirty-one per cent had invasion of the prostate and 40 per cent had vesicle involvement. Ewert (4) found that 15 per cent of his patients had carcinomatous extension to the bladder or prostate, either at the time of surgery or as delayed recurrence. Ganem recently reviewed this problem and states, "Rectal carcinoma may spread locally to involve the prostate and seminal vesicles without producing distant metastases." He presented the history of a patient with rectal carcinoma and local microscopic invasion of the prostate treated by combined resection plus total prostatectomy and seminal vesiculectomy. The patient is well and without evidence of recurrent tumor or urinary symptoms 5 years later. Campbell has emphasized the need for total prostatectomy and cautioned against shaving a portion of the prostate to remove adherent tumor. This latter procedure frequently causes partial sloughing of the prostate and fistula formation, an important fact to remember. The percentage of carcinomas near or attached to the prostate in this series was 21 per cent, an impressive figure. In 25 per cent of these patients there was invasion of the pericolic fat and in 1 a perforation over the prostate. No information regarding prostatic involvement is available.

When the carcinoma is over, near, or attached to the prostate or seminal vesicles, the logical therapy is removal of the prostate and seminal vesicles en bloc with the rectum. This procedure serves 3 major purposes: It eliminates the usual postoperative urinary difficulty, eliminates urinary tract infection, and it removes the area of possible direct carcinomatous involvement or extension. Of course, the morbidity may be increased,

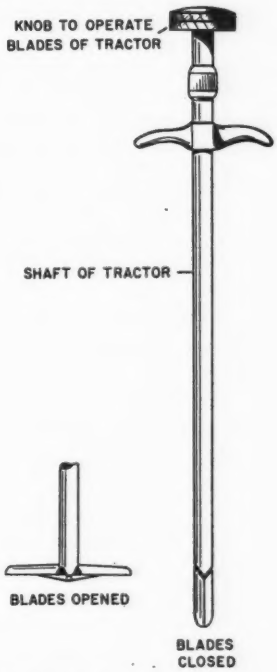


FIG. 6. The straight Lowsley retractor.

but if performed when indicated, local recurrences may be reduced.

Technically, we believe the prostate should be approached first through the usual perineal incision. When the apex of the prostate is exposed, the distal urethra is severed and the apical portion of the prostate is left. The prostate and seminal vesicles are freed in the usual manner and severed from the bladder base. Following this step, the rectum is dissected free and removed en bloc with the prostate and seminal vesicles. Continuity of the urinary tract is re-established by suturing the bladder neck to the apex of the prostatic urethra. By leaving the apex of the prostate a watertight closure and urinary continence are insured.

DISCUSSION

Because of significant (18 per cent) prostatic obstruction following abdominoperineal resection in a 5 year period at this

hospital, simple perineal enucleation of the prostate is preferred at the time of the combined resection in patients with significant prostatic enlargement. This procedure is not a total prostatectomy requiring vesicourethral anastomosis but a simple prostatotomy, enucleation of the prostatic adenoma, and a careful watertight enclosure of the small prostatotomy incision (see Figs. 1, 2, 3, 4, and 5). We believe that this procedure may result in fewer postoperative urinary complications and reduce the necessity for further urologic operations.

Local recurrences of carcinoma of the rectum regardless of the location of the carcinoma involve the prostate, bladder, and/or seminal vesicles in at least 10 to 15 per cent of the operable patients. Forty to 50 per cent of all patients with carcinoma of the rectum showed recurrences in these areas at postmortem. Partial excision or shaving of the posterior prostatic tissues to remove adherent tumor is strongly condemned because of possible slough and fistula formation. Total prostatectomy and seminal vesiculectomy are proposed only when the carcinoma is over, near, or attached to the prostate or seminal vesicles. We believe that this procedure can lessen recurrence of carcinoma in these areas and will certainly eliminate postoperative urinary obstruction. To avoid complications, careful and skilled technique is required to perform this operation. If it is done carefully, no undue complications should occur.

SUMMARY

1. A report of 62 patients following abdominoperineal resection with reference to postoperative urinary retention is given.

2. Eighteen per cent of the patients required prostatectomy because of postoperative urinary retention.

3. Thorough preoperative and postoperative urologic evaluation is emphasized.

4. Perineal enucleation of obstructive prostatic adenoma at the time of abdominoperineal resection is proposed.

5. Local extension of the prostate and seminal vesicles by rectal carcinoma is emphasized.

6. Total prostatectomy and seminal vesiculectomy, en bloc with rectal specimens, are proposed for lesions over, near, or attached to the prostate.

REFERENCES

1. Bacon, H. E., and McCrea, L. E. Abdominoperineal proctosigmoidectomy for rectal cancer; management of associated vesical dysfunction. J. Am. M. Ass., 1947, 134: 523–526.
2. Campbell, E. W., and Gislason, G. J. Urologic invalidism following abdomino-perineal rectosigmoidectomy. Ann. Surg., 1950, 132: 85–93.
3. Emmett, J. L., and Cristol, D. S. Urinary retention following surgical operation on rectum and sigmoid; treatment by transurethral resection. J. Am. M. Ass., 1944, 126: 1077–1079.
4. Ewert, E. E. Comparative analysis of urologic complications following large bowel surgery. J. Urol., Balt., 1941, 46: 764–776.
5. Idem. Urologic complications following large bowel surgery and their management. Surg. Clin. N. America, 1946, 26: 695–702.
6. Flint, G. W., Hermann, H. B., and Ritstein, C. B. The mechanism of bladder dysfunction following abdomino-perineal resection of the rectum. Surgical Forum 1950; American College of Surgeons. Vol. I, pp. 140–148. Philadelphia and London: W. B. Saunders Co., 1951.
7. Ganem, E. J. Rectal carcinoma invading the prostate gland. Arch. Surg., 1957, 75: 85–89.
8. Kickham, C. J. E., and Bruce, N. H. Urologic complications in malignant disease of the rectum. J. Urol., Balt., 1939, 41: 541–556.
9. Marshall, V. F. Observations on urinary dysfunction after excision of the rectum. J. Urol., Balt., 1946, 55: 409–416.
10. Oppenheimer, Gordon. Late invasion of bladder and prostate in cancer of the rectum or rectosigmoid following abdomino-perineal resection. Ann. Surg., 1943, 117: 456–467.

REDUCED METABOLISM BY MEANS OF HYPOTHERMIA AND THE LOW FLOW PUMP OXYGENATOR

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INTRACARDIAC SURGERY to be safe and practical must not depend primarily on the manual dexterity of the operating surgeon. To permit proper intracardiac procedures to be carried out, it must be possible to have prolonged direct vision access to the entire interior of the heart. During this time, adequate oxygenated blood must be provided to the brain and other vital organs. Although very satisfactory pump oxygenators, supplying essentially a full basal blood flow, are now available, the apparatus is cumbersome, complicated, and expensive. Many surgeons are endeavoring to "get by" with lower flows and shorter periods of time, despite the inherent dangers of this parsimonious approach. The great reduction in oxygen demand brought about by cooling, has led to the development of fairly practical procedures utilizing immersion hypothermia. If hypothermia alone is used, however, there is always the danger of irreversible arrhythmia or cardiac failure. For this reason a few clinical workers are now combining the use of a pump oxygenator with immersion hypothermia. Although this offers certain advantages, the method is unusually cumbersome and considerably prolongs the anesthetic and operative procedures. Immersion cooling is inefficient since the vital organs are cooled only after the skin and muscles are markedly reduced in temperature. Furthermore, superficial necrosis may result. We have been experimenting with the combination of hypothermia and a low flow pump oxygenator since 1953 (8, 10) and believe that we have developed a practical system of combining these two methods. Economy of time and equipment is brought about by direct cooling of the blood as it passes through the pump oxygenator circuit. Direct cooling by means of the extracorporeal circuit provides remarkable saving in the amount of heat that must be extracted because the blood goes primarily to the high flow rate organs which are those having the greatest need for oxygen. These are then cooled rapidly and the maximum decrease in oxygen demand is brought about. So little cooling is required, in fact, that actual warming of the blood appears to be unnecessary. To the present time, we have no evidence of any deleterious or irreversible effect of the cooling itself. This practical low flow method permits use of a small extracorporeal pump oxygenator of simple design, less difficult cannulation procedures, and a reduction in total blood trauma.

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METHOD

Mongrel dogs weighing between 10 and 15 kilograms were premedicated with 200 milligrams of demerol hydrochloride and 0.4 milligram of scopolamine hydrochloride. They were anesthetized with an intravenous drip of pentothal sodium and connected to a pump oxygenator circuit as shown in Figure 1. Heparin sodium, 4 milligrams per kilogram, was given just prior to cannulation. Polyvinyl or stainless steel cannulas of a size suitable for the vessels were used for the azygos vein and for the femoral artery and

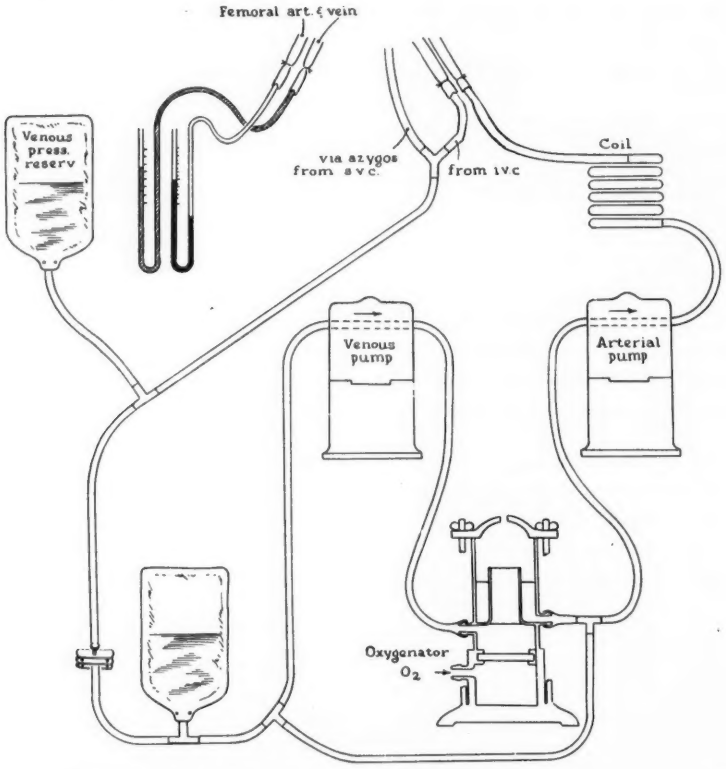

FIG. 1. Blood is collected by gravity from cavae (*s.v.c., i.v.c.*) and pumped through small bubble oxygenator by venous pump. This is run a little slower than arterial pump so that some blood will pass through shunt unoxygenated and join the blood going to the animal, thus reducing the arterial oxygen tension from a high to a normal level. The blood passes through a stainless steel heat exchange coil before going to the femoral artery. Venous pressure is read on a saline manomoter connected to the femoral vein and is kept within normal limits by raising or lowering the venous pressure reservoir. Screw clamp regulation maintains a constant level in the oxygenator and the gravity reservoir (often omitted) stabilizes the flow, and provides reserve blood. Pump settings are not changed; 100 per cent oxygen (O_2) is employed.

vein. Polyvinyl tubing was used in the circuit. The heat exchanger was a stainless steel coil, 3/16 inch inside diameter and 7 feet in length. A fibrin trap of stainless steel mesh was generally employed. Most of the experiments were done with one of several small bubble oxygenators, the most satisfactory of which was one designed by Gollan. Antifoam A was used for defoaming of the blood. Glass parts of the oxygenator were siliconed. A screen oxygenator was used in some experiments as was also a disposable large bubble oxygenator. In order to eliminate possible denaturing effects of the oxygenator on blood, a series of experiments was carried out utilizing a homologous lung. The arrangement of the circuit is shown in Figure 2 (10). Blood for priming and transfusion was collected from anesthetized dogs into siliconed bottles containing 15 to 20 milligrams of sodium heparin.

Venous pressure was measured by means of a saline manometer inserted into the inferior vena cava. The aortic pressure was

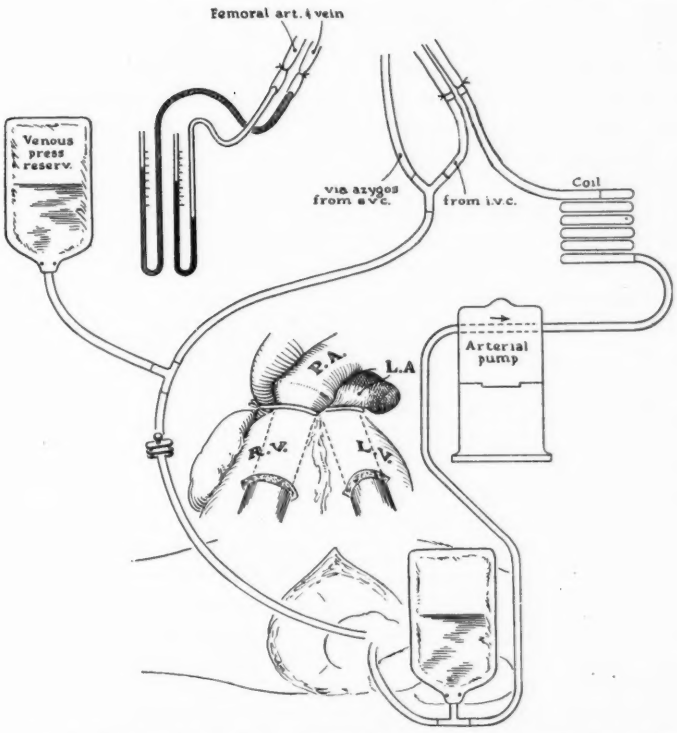

FIG. 2. The circuit is similar to the one shown in Figure 1, except that a dog heart and lung in situ have been substituted for the small bubble oxygenator, the shunt and the venous pump have been eliminated, and the gravity reservoir has been moved from the venous side of the oxygenator to the arterial side. This reservoir is essential. By providing constant low pressure egress of blood from the lung it prevents pulmonary edema. The cannulation is extraordinarily simple. The donor dog is heparinized and bled. The chest is opened transsternally. Two heavy cords are passed through the transverse sinus by hand. One is tied about the pulmonary artery (*P.A.*) and aorta to retain a flared cannula inserted through the right ventricle (*R.V.*) into the *P.A.* The second is swung over the cardiac apex and tied above the atrioventricular sulcus to retain a cannula inserted through the left ventricle (*L.V.*) into the left atrium (*L.A.*). A pneophore respirator is used for rhythmic lung inflation.

recorded by means of a mercury manometer or a strain gauge and a Sanborn recorder. Temperatures were measured by means of thermisters of suitable type. An electrocardiogram was occasionally made. An estimate of changes in blood volume was secured by weighing the reservoir bags of the extracorporeal circuit. The blood volume itself was determined preoperatively and postoperatively by an albuminated human serum albumin method. Blood oxygen was determined by the Van Slyke method. A Beckman meter was used to determine the *p*H of the blood. Blood flow was measured by a rotameter or by using a calibrated pump. The following additional hematologic and chemical determinations were carried out: plasma hemochromogen, hematocrit, total red count, total white count, total platelet count, total and fractional proteins, and whole blood carbon dioxide.

Heparin neutralization was generally carried out with one-half to three-quarters of the calculated dose of protamine, calcu-

lated milligram for milligram. To produce cardiac standstill, a rapid injection of 20 cubic centimeters of oxygenated blood at room temperature containing 2 cubic centimeters of 25 per cent potassium citrate was made into the clamped ascending aorta. Animals in survival experiments were given 300,000 units of penicillin at the completion of the procedure; otherwise, ordinarily no drugs were administered. On occasion, calcium gluconate, neosynephrine hydrochloride, cedilanid, isuprel hydrochloride, and nalline hydrochloride have been administered.

The extracorporeal circuit was primed with fresh heparinized whole blood. Blood was collected from the inferior and superior venae cavae by gravity equal to 50 to 60 centimeters of water. Arterial pump flow was generally preset and then not changed, venous flow being regulated by the screw clamp on the venous line. The venous pressure was kept at a constant "normal" level by varying the position of the venous pressure bag connected to the upper part of the venous line. Cooling was effected by immersing the cooling coil in agitated ice water and a 40 degree C. water bath was used for warming. There was no accurate measurement of blood loss, and the dog's postoperative blood volume was brought to approximately normal by adjusting the venous pressure to its preoperative level. Confirmation of the approximate blood volume adjustment was secured by weighing the animal. External warming, as desired, was brought about by placing an ordinary heating pad underneath the animal.

More than a hundred experiments have been carried out by utilizing a pump oxygenator in conjunction with hypothermia. In the earliest work (10), the heart was not excluded from the circulation, and the extracorporeal circuit constituted a partial cardiac bypass only. Later, the heart was excluded after cooling had been completed, the extracorporeal circuit thus being initially a partial cardiac bypass and later a total cardiac bypass. Recently, we have experimented intensively with complete cardiac bypass concomitant with cooling. In 12 experiments, the animals were maintained at normal temperature during total bypass. Total bypass periods have most usually been 30 minutes, but periods as long as 3 hours have been studied occasionally in conjunction with cooling.

An attempt was made in the majority of the experiments reported herein to maintain the blood flow at about 30 cubic centimeters per kilogram, although not infrequently in some of the earlier work variations in venous pressure produced considerable deviation from this.

In many experiments, no attempt was made to secure survivors. For example, when recording the temperature of the brain, the thermister was introduced into the cranial cavity via a large bore needle, driven through the orbit with a hammer, and since the animals had been on heparin, it was presumed that survival would be unlikely and undesirable and the animals were therefore sacrificed.

RESULTS AND DISCUSSION

Boerema reported the use of blood stream cooling in 1951. Gollan and his associates reported in 1952 cooling and warming of the entire circulating blood volume of dogs using a simple silver coil in a pump oxygenator circuit (7). He did not at that time note any difference in the cooling rate of different portions of the animals but has recently confirmed the differential nature of the cooling process (6). Extensive experimental studies in this field have been carried out by Gollan in recent years. His particular interest has been the use of temperatures near 0 degrees C. Clinically, Ripstein and associates and Sealy and associates (13) have utilized the combination of externally induced hypothermia with a pump oxygenator. Following the work of Delorme, Brock and Ross have utilized direct blood stream cooling (venovenous) without a pump oxygenator in clinical cases. The subject has recently been reviewed by Dammann and Muller.

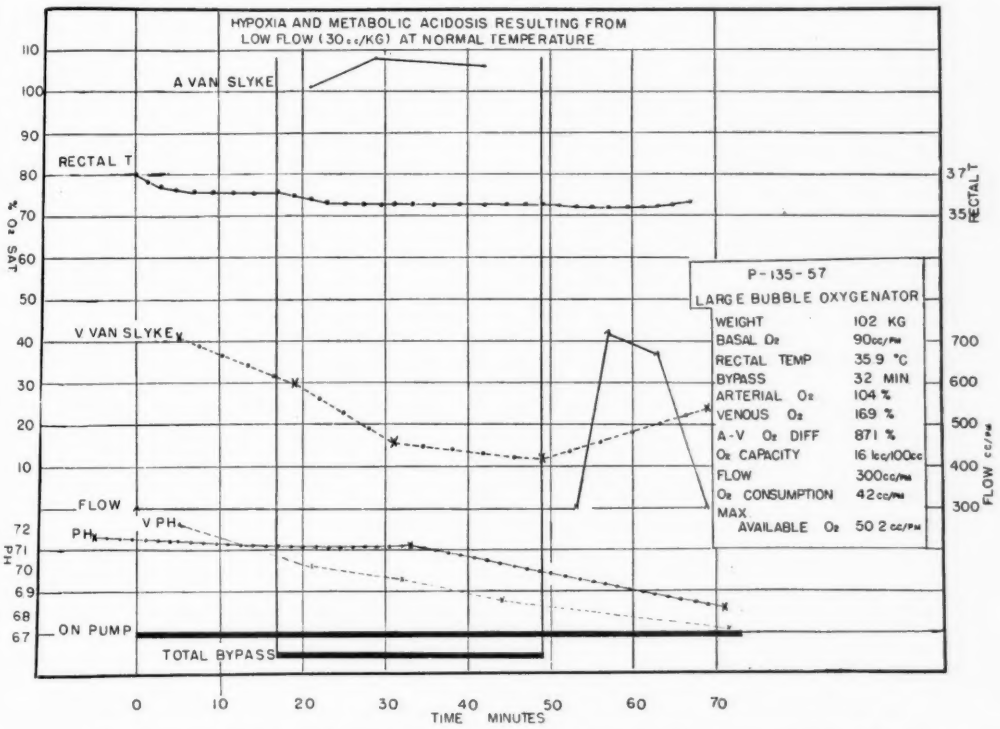

FIG. 3. Despite high arterial oxygen saturation, low blood flow at normal temperature results in a marked drop in venous oxygen saturation and progressive acidosis. Since the *p*H drop is not reversed by a higher flow and hyperventilation after the bypass, it is assumed to be metabolic and not respiratory in origin. A sizable oxygen debt is incurred during the bypass.

Other workers appear to have approached the subject quite differently than we have. The following paragraphs and accompanying charts and tables summarize the basic findings of our work.

Low blood flow at normal temperature. Extracorporeal blood flows in the neighborhood of 20 to 25 per cent of a dog's basal cardiac output have resulted in hypoxia and metabolic acidosis when employed at normal temperatures. Figure 3 is illustrative of our average data. The basic oxygen demand in this 10.2 kilogram dog was about 90 cubic centimeters per minute, but even total extraction of oxygen from the arterial blood would have left a significant deficit of about 40 cubic centimeters of oxygen per minute. The dog's effort was efficient, and 42 of an available 50 cubic centimeters of oxygen per minute were extracted, leaving a deficit of approximately 50 cubic centimeters per minute, or 1,500 cubic centimeters for the bypass of 30 minutes. Although such oxygen deficits can apparently be tolerated without irreversible damage, they result in considerable metabolic disturbance, probably as a result of extensive anaerobic metabolism. Despite hyperventilation with a large bubble oxygenator and increased flows after the total bypass, *p*H values fell, suggesting a substantial metabolic acidosis. Extracorporeal flows in this neighborhood are probably safe only for relatively brief periods of time, and we believe they should not seriously be recommended for human use except in an emergency or when the surgeon knows he

TABLE I.—ORGAN BLOOD FLOW CALCULATIONS BASED ON COOLING DATA FROM FIGURE 4

Organ	Weight, gm.	Basal flow per 100 gm. c.c. per minute*	Cooling rate °C. per minute	Flow rate per 100 gm. c.c. per minute	Flow rate of whole organ c.c. per minute†
Heart	135	70	1.6	22	30
Kidney‡	119	430	3.0	41	49
Liver	630	80	1.6	22	138
Brain	135	54	0.75	10	13
Muscle§	8100	7	0.167	2	185
	Average	11.6		Average 2.3	Total 415

Calculated from period of most rapid cooling. Dog weight 18 kgm. Flow rate 415 c.c. per minute or 23 c.c. per kgm.
*Medical Physics. Vol II, pp. 244–245. Chicago: Year Book Publishers, 1950.
†Arbitrarily assumed that entire flow was directed to these organs. At normal temperature this would introduce about a 15 per cent error.
‡Substantially higher rates of cooling have been recorded in some experiments. Flow rates were unusually low in this experiment. Although renal flow was reduced to less than one-tenth, this should be adequate for oxygenation if not for urine formation.
§Because of cooling by room air, calculated flow is probably too high.

TABLE II.—ORGAN TEMPERATURE DATA WITH PARTIAL BYPASS AND FLOW RATES OF 25 TO 30 CUBIC CENTIMETERS PER KILOGRAM

Weight, kgm.	Minutes to cool heart to 20° C.	Brain	Liver	Kidney	Rectum	Muscle
12	30	23.6		19.0	26.0	19.8 FL
22	38	20.4	21.2		26.6	26.4 HL
12	22	21.0		22.4	29.0	
13	12	18.0	28.0		33.6	28.2 FL
15.5	12	19.0	24.0		33.0	33.2 FL
11.8	18		21.6	20.0	27.9	
8.9	12		24.8	20.2	27.7	
18.8	25		21.7		25.4	27.9 HL
21.7	23			21.0	29.8	30.2 HL
12.5	15		20.7		24.2	32.4 HL
Average 14.8	20.7	20.0	23.1	20.5	28.3	28.2

On the average intrapericardial and esophageal temperatures differed by only 0.3° C., so that generally, for convenience, only the temperature of the esophagus at the level of the heart was measured.
FL—foreleg; HL—hindleg.

TABLE III.—ORGAN TEMPERATURE DATA WITH TOTAL BYPASS AND FLOW RATES OF 30 CUBIC CENTIMETERS PER KILOGRAM

No.	Wt., kgm.	Minutes to cool esophagus to 20°C.	Brain	Liver	Kidney	Rectum	Muscle
140-57	9.5	11				31.0	
159-57	9	14	22.0	24.2	21.6	30.0	
168-57	12.7	6				28.0	
173-57	18	20	24.4	26.8	20.0	33.0	33.4
176-57	13.5	13	23.4	20.0	18.0	31.0	32.0
184-57	13.4	4				32.0	
185-57	11.8	13	18.0	23.6	18.0	29.4	27.0
192-57	13	8	26.4	25.2	21.4	33.0	
232-57	13.6	5				26.0	
20-58	11	6				36.0	
Average	12.6	10	22.8	24.0	19.8	31.9	30.8

Variations in cooling rates are due primarily to the way the heat exchange coil was handled. For rapid cooling the coil was fully immersed and agitated. At other times it was not agitated or was only partially immersed. Arterial in-flow temperatures consequently varied from about 7 to 18 degrees C.

can do the intracardiac procedure with great speed.

Differential organ cooling (*heat exchange*). By cooling the blood just before returning it to the animal, marked reduction in the temperature of such vital high flow rate organs as the heart, brain, liver, and kidney[1] has been produced easily with great economy of total caloric transfer, since the great bulk of the animal (skin, muscle, and bone) has been cooled much more slowly. This observation is illustrated in Figure 4. Here a flow rate of only 23 cubic centimeters per kilogram was used with the animal on total bypass. There was a marked differential in the cooling rates of the various organs,

[1]These organs, weighing about 5 per cent of the total, normally receive about 60 per cent of the animal's basal blood flow.

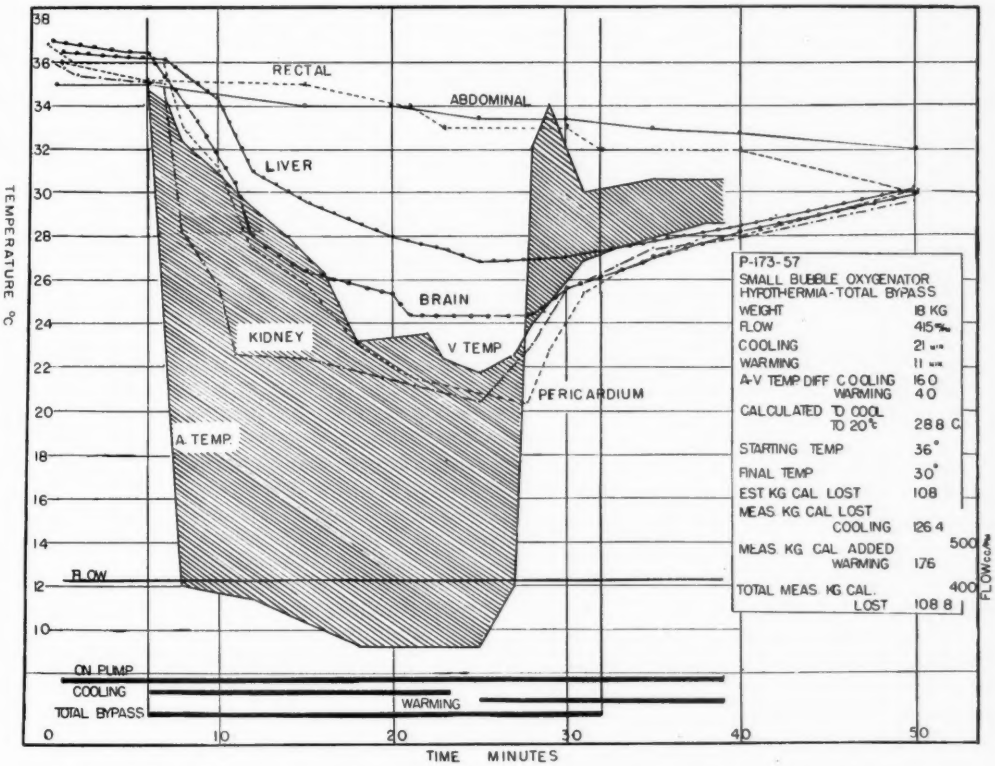

FIG. 4. Organ cooling and caloric data during a total bypass experiment: The larger shaded area is bounded above by the venous outflow temperature and below by the arterial inflow temperature. This arteriovenous temperature difference times the flow permits easy estimation of the caloric exchange in cooling. The smaller shaded area is bounded above by the arterial and below by the venous temperature and therefore represents warming. Various organ temperatures are indicated separately.

varying from 0.167 degrees C. per minute for muscle to 3 degrees C. per minute for the kidney (Table I). Data showing relative organ flow rates for the dog are given for comparison. Cooling data for partial and total bypass are recorded in Tables II and III. It is readily seen that the cooling rates are related to the relative flow rates. It should be noted that if immersion cooling had been utilized to bring the vital organs to 20 degrees C., at least 288 kilocalories would have had to be extracted, whereas, in actual fact the kilocalorie loss was only 126. A similar situation would obtain in the human being when, for example, a 60 kilogram man with a basal blood flow of 5,470 cubic centimeters per minute would have a flow of 3,520 cubic centimeters per minute for the heart, liver, kidney, and brain, though they weigh but 3.5 kilograms. These organs, therefore, would be cooled very quickly on total bypass even with a small blood flow rate (Table III). Less striking differential cooling rates are generally obtained with partial bypass (Table II).

The warming process. Warming was greatly facilitated by the heat stored in the nonvital areas, so that very little heat needed to be added before the extracorporeal circuit was

TABLE IV.—COOLING DURING 30 MINUTE TOTAL BYPASS WITH 30 CUBIC CENTIMETERS PER KILOGRAM FLOW CALORIC EXCHANGE AND OXYGEN CONSUMPTION DATA

No.	*Wt., kgm.*	*Duration cooling, minutes**	*Calories removed†*	*Lowest arterial pH‡*	*A-V oxygen difference, per cent*	*O_2 used, c.c. min.*	*Estimated basal O_2§ consumption*	*Per cent O_2 saving*	*Mean reduction, body temp., °C.*
140-57	9.5	18	65	7.27	41	22	85	75	7
184-57	13.4	7	100	7.1	66	35	109	68	7.5
191-57	12.9	8	90	7.14	48	32	107	70	7
195-57	12.9	7	78	7.39	52	38	107	65	6
225-57	13.2	7	106	7.15	54	39	108	64	8
231-57	13	10	101	—	53	36	107	64	8
232-57	13.6	7	82	—	47	31	110	62	6
238-57	11.8	10	83	7.38	48	31	100	69	7
241-57	15.4	10	105	7.52	45	43	119	64	7
13-58	9.5	10	60	7.22	53	26	85	69	6.5
Average	12.5	9.4	87	7.27	50.7	33.3	103.7	67	7

*Time heat exchange coil was in ice water. Cooling is somewhat longer than this.
†During entire bypass most of the exchange is during the actual time heat exchange coil is in ice water but depending on room temperature, moderate cooling occurs during entire bypass. Above figures are from estimates of average temperature before and after cooling.
‡All *pH* levels below 7.2 are in experiments in which CO_2 elimination was too low.
§Basal oxygen figures are based on best data from various sources. No allowance has been made for individual variations or for the effect of the light anesthesia employed. Oxygen consumption of similar animals held at normal temperature might have greater validity.

discontinued. In the more recent experiments, it has been our practice not to provide any extracorporeal warming at all because of the possible danger of liberating oxygen bubbles, and this has not interfered materially with the advantages of the method. In Figure 4, it can be seen that the arteriovenous temperature difference multiplied by the flow in liters equaled the heat exchange in kilocalories. Since the initial average temperature was about 36 degrees C., the final temperature 30 degrees C., and the dog's weight 18 kilograms, the net caloric loss was only 108 kilocalories. This final temperature was made possible with the addition of only about 19 kilocalories during warming, yet the vital organs had the metabolic protection of much lower temperatures, averaging about 22 degrees C. If the entire dog had been cooled to this extent, the extraction of 252 kilocalories would have been required and this would have necessitated extensive rewarming before artificial respiration could have been discontinued.

Oxygen saving through lowered metabolism. Rapid cooling of the internal organs resulted in a marked reduction of the arteriovenous oxygen difference. Even with a low flow rate of 30 cubic centimeters per kilogram, the venous oxygen saturation often rose during the procedure while at the same time the total oxygen consumption fell to as little as 25 per cent of the basal estimated oxygen requirement. That the cold animal is able to extract oxygen from the blood efficiently was shown in an experiment using a teflon membrane of inadequate size. The arterial oxygen saturation fell progressively to 47 per cent and averaged only 65 per cent. Nevertheless, this animal was able to extract 19 cubic centimeters of oxygen per minute by progressively dropping the venous oxygen to 26 per cent. He was a survivor. Relatively short periods of cooling have proved adequate to bring about great oxygen saving. More prolonged cooling produces decreasingly less oxygen-saving, and since it may leave the animal too cold to breathe well without assistance it is to be avoided. Figure 5 illustrates 2 properly conducted experiments which have been combined to give more complete data. A 10 minute period of cooling was used and this produced an estimated oxygen saving of 64.5 per cent. It would appear that the oxygen saving is essentially due to the antimetabolic effect of the cooling rather than to inadequate perfusion of certain portions of the vascular bed. This concept is suggested by the stability of the arterial and venous *pH* values which would not be expected in the presence of significant anaerobic metabolism and metabolic acidosis. The rise in venous oxygenation during the procedure should be noted. Internal warm-

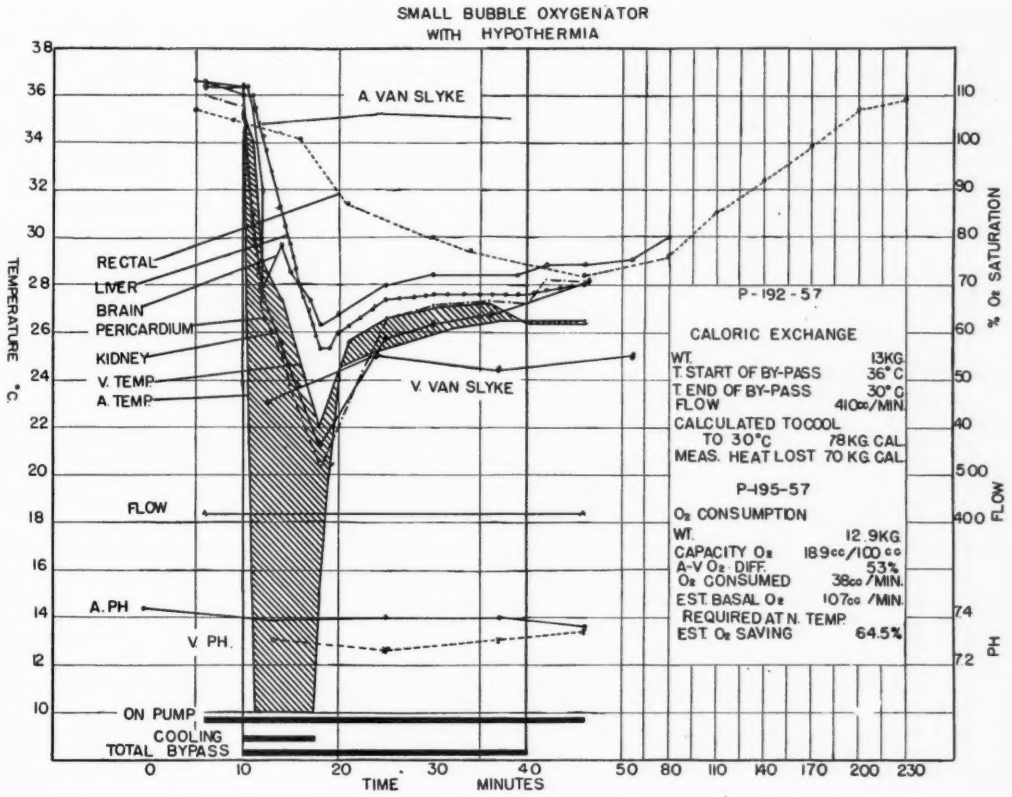

FIG. 5. Two experiments on similar dogs are combined in this chart to provide a more complete picture of the physiologic changes. Heat exchange is indicated by the shaded area as in Figure 4. Arterial and venous oxygen saturation data and blood *p*H levels have been added. After bypass, warming was brought about by external application of heat (heating pad) assisted by shivering of the animal. A 10 minute period of cooling permitted maintenance of normal venous oxygen saturations and *p*H levels even though blood flow was only 25 per cent of normal (30 c.c. per kgm.) (Fig. 3). The heart was available for surgery during the entire bypass period. It has been possible to prolong the bypass to 60 minutes with no additional cooling and very little deterioration in the venous oxygen saturation or *p*H.

ing was not utilized in this procedure, as slow external warming has proved to be entirely satisfactory.

Ten total bypass experiments are summarized in Table IV. It is readily seen that on the average the arteriovenous oxygen difference and the *p*H levels remained very close to normal. At the same time, 9.4 minutes of cooling led to a final body temperature only 7 degrees below normal, making possible an average oxygen saving of 67 per cent. Although a bypass time of 30 minutes was chosen for these experiments, it has been possible safely to continue the bypass for 30 additional minutes without additional cooling or increase in flow rate.

Further cooling is less effective in reducing over-all metabolic needs. Table V shows data from experiments in which total bypass was not begun until the esophageal temperature had reached approximately 20 degrees C. This requires about 20 minutes

of cooling or twice that of the animals shown in Table IV and thus means much greater caloric exchange also. The arteriovenous oxygen difference is, however, identical; there is only a small difference in the oxygen consumption; and only a 5 per cent improvement in the oxygen saving.

Comparison of partial and total bypass. Cooling has been accomplished during both partial and complete bypass. A comparison of the 2 methods follows:

COOLING BY PARTIAL BYPASS

Advantages:

1. Peripheral cannulation is possible.
2. Thoracotomy may be delayed.
3. Cooling or warming may safely be done slowly.
4. Simple assistance of a failing circulation is possible.

Disadvantages:

1. The duration of extracorporeal circulation must be considerably in excess of the period of total bypass if one is used.
2. It is sometimes difficult to get any but relatively low blood flows because of the competition with the heart for blood.
3. Because of limitations in flow rate, rapid cooling is more difficult to obtain than with total bypass.
4. Intermediate rates of cooling may have a deleterious effect on the cardiac output and on the blood pressure.
5. Arterial cannulation must permit blood to flow into the aortic arch to prevent purely regional cooling.

COOLING BY TOTAL BYPASS

Advantages:

1. The entire period of extracorporeal circulation may be used for bypass.
2. Since rapid cooling is possible, the metabolic need for oxygen is also lowered rapidly.
3. When rapid cooling rates are used, a given metabolic saving is achieved with a minimum caloric exchange.
4. Arterial cannulation need only direct blood into the aorta. It need not be directed into the aortic arch.
5. With a constant total blood flow through the extracorporeal circuit, it is possible to measure relative organ blood flow rates by changes in organ temperature.

Disadvantages:

1. Thoracotomy must be done before the extracorporeal circuit is started.
2. With low flows cooling must be rapid because the heart is not permitted to contribute to the total flow.
3. With very low flows it may be wise to use vasopressor drugs to maintain the blood pressure.

Since complete bypass is generally utilized for intracardiac surgery and since it is to be preferred from the standpoint of collecting analyzable data, most of our reported results were obtained from experiments utilizing complete bypass either during or following cooling.

An example of organ flow calculations that can be obtained are given in Table I. The figures are crude and more accurate measurements using slower cooling rates would be preferable. Higher flow rates approaching normal basal values might considerably change the proportionate flows shown here. By measuring the flow of a single internal organ, however, as by rotameter, and recording the temperature changes in other organs, such as the adrenal, relative flows of organs difficult to study could be worked out. If the subject were placed in a constant temperature room, accurate differential flow rates of superficial tissues could also be determined. The muscle cooling for instance, though slow, is greatly influenced by the ambient room temperature. Flow rates of muscle calculated from this experiment are consequently probably too high.

Survival. Survival results were disappointing when the small bubble oxygenator was used. The reason for this was not immediately evident as oxygenators of similar design have been very satisfactory in clinical use in some hands. Our major difficulty was an unexplained bleeding tendency which resulted in death some hours after completion of surgery. Routine survivors were easily secured when the only surgical procedure was a simple thoracotomy, but whenever intracardiac surgery had been performed, there were no survivors. Substitution of the homologous lung for the small bubble oxygenator, however, resulted in almost routine survival, and no difficulties were encountered from bleeding in this group. No improvement occurred when the disposable large bubble oxygenator was employed in a few experiments. Excellent results have also been obtained in a small

TABLE V.—OXYGEN CONSUMPTION DURING LOW FLOW WITH HYPOTHERMIA AND DURING TOTAL CARDIAC BYPASS

No.	Wt., kgm.	Est. basal O_2 c.c. min.	Average esoph. temp. °C.	Average rectal temp., °C.	Bypass time, minutes	Arterial O_2 saturation	Venous O_2 saturation	A-V O_2 diff.	Flow c.c. min.	O_2 cons. c.c. min.	Per cent est. O_2 cons.
P-98-57	10.1	94.5	25.	29.	53	98	63.5	34.5	360	19.8	20.9
P-100-57	13.2	107.5	21.	25.	30	98	45.	53.	550	45.	42.
P-101-57	13.6	110.	21.5	27.	30	95	51.	43.	440	29.	26.4
P-105-57	13.4	109.	21.5	24.5	44	87	46.	41.	430	23.7	21.6
P-115-57	12.	101.5	20.5	25.5	31	99	59.	40.	390	23.3	23.
P-128-57	10.7	93.	23.5	28.5	43	95	40.	55.	350	30.5	32.8
Average	12.3	102.6	22.2	26.6	38.5	95	50.7	44.4	420	30.1	27.8

group in which the screen oxygenator has been used. This oxygenator appears suitable for clinical use but has much too large a priming volume to be used easily in routine laboratory work. We are currently experimenting with a teflon membrane oxygenator and believe that this will be suitable for both clinical and experimental purposes. Survival experiments in 10 to 12 kilogram dogs have been possible using very small areas of 0.5 mil teflon. This work will be reported later.

Arterial and venous pressures, blood volume. Blood flow rates of 20 to 25 per cent of the normal basal rate have generally resulted in an adequate arterial pressure. During the induction of hypothermia the arterial pressure has usually fallen to about 30 to 50 per cent of the preoperative level and has then risen slightly as the animal reaches a more homogeneous temperature. Pressor drugs have been needed occasionally when oxygenation or carbon dioxide elimination was inadequate. It has been possible to maintain the venous pressure at a very constant level by means of the venous pressure reservoir. This has also provided a valuable way of adjusting the blood volume, which will be reported elsewhere (9). Preoperative and postoperative blood volumes and weights have shown no large discrepancies.

Chemical and hematologic data. It is not possible to analyze all of the chemical and hematologic data at this time. Much of it appears related more to the particular type of oxygenator than to the effects of cooling. In general, there have been no significant alterations in plasma proteins, *p*H, or blood formed elements related to the cooling per se. There has been a consistent sizable drop in the platelet count with all types of oxygenators whether the subject was cooled or not. There have been small changes in some of the protein fractions, especially the albumin, but again this has not apparently been related to the cooling. Fibrinogen has not been greatly affected. Clotting was delayed and the clot was of poorer quality when the small bubble oxygenator was used than when the homologous lung or the screen oxygenator was used, but these changes have not been sufficient to account for the bleeding tendency noted. Cooling has produced no irreversible electrocardiographic, blood pressure, or reflex changes. In many experiments, a small reversible increase in blood volume was associated with cooling.

Potassium arrest. Since a considerable degree of cooling generally occurs in the isolated heart of the normothermic animal by virtue of its exposure to room air and since cardiac isolation has generally been carried out in our experiments before cooling has been started, the state of the heart during bypass has not been particularly influenced by the hypothermia. At the completion of bypass, however, when the aortic clamp is removed the heart has usually received blood at 28 to 30 degrees C. rather than at body temperature. Generally, the heart has resumed a strong beat quickly and has not required drugs. At other times, there has been a temporary heart block apparently reversed by small doses of intravenous isuprel hydrochloride. At other times a readily revertible ventricular fibrillation

has occurred. In general, potassium citrate arrest has been satisfactory in our hands but this maneuver appears not to be without some danger. The problems of potassium arrest in the hypothermic dog heart are discussed by Sealy (14).

Cardiac irritability. Irritability of the heart has not been a problem except when fibrillation has occurred during total bypass. In this situation if there is not immediate decompression of the heart the pressure in the pulmonary vessels soon reaches that of the aorta and severe hemorrhagic pulmonary edema ensues. This problem is related to the necessary techniques of intracardiac surgery and is readily soluble. Ventricular fibrillation during partial bypass or on completion of potassium arrest has not been difficult to revert. We prefer the use of electric shock to reversion with potassium citrate.

Comparison of blood stream and immersion cooling. Immersion cooling also produces temperature gradients within the animal but these are quite the reverse of those obtained by direct cooling of the blood. In external cooling, the less vital portions of the body, the skin, subcutaneous tissue, and muscle are cooled most greatly. On cessation of external cooling the internal temperature continues to fall for a variable and uncontrollable period of time, whereas, in cooling of the blood the internal temperature rises when cooling has stopped and this can be prevented readily when it seems to be undesirable.

It is of interest that anesthesia sufficiently deep to prevent shivering is necessary for external cooling below about 32 degrees C. while shivering is not produced in animals internally cooled even when minimal anesthetic doses are used. Internally cooled animals regularly shiver when their internal temperature approaches 28 to 30 degrees C. during the rewarming and this greatly increases the rewarming rate. Externally cooled animals usually exhibit markedly depressed respirations and reflexes below 25 degrees C. Those internally cooled may show strong respiratory and reflex activity with internal (brain) temperature near 20 degrees C. End organ refrigeration (cold narcosis) may be the cause of depression in externally cooled animals.

Internally cooled animals show other differences also suggesting that the physiologic study of hypothermia should be broadened to include cooling produced by a variety of methods. Unless observed changes are found to occur generally with cooling they should not be considered characteristic of hypothermia.

CONCLUSION

The overwhelming weight of present evidence is that the cooling process is quite reversible. It appears practical and offers a number of significant advantages. Its possible disadvantages are mainly theoretical. Both advantages and disadvantages are summarized.

The advantages are as follows:

1. A combination of hypothermia and a pump oxygenator permits the use of a small and simple apparatus and low blood flow rates.

2. Since flow rates are low, cannulation procedures may be simplified, and peripheral vessels may be utilized routinely.

3. A small caloric exchange is all that is required to produce a large decrease in oxygen demand. For this reason the method is much more efficient than immersion hypothermia.

4. The lowered total extracorporeal flow should result in a decrease in the total damage to the blood passing through the pump oxygenator.

5. In very sick or moribund patients it should be possible to assist the failing heart without or prior to thoracotomy and to do this with a small and perhaps readily transportable piece of equipment.

The possible disadvantages are as follows:

1. Cold per se may produce some qualitative changes in cellular metabolism which are deleterious. Present knowledge of enzyme systems and studies carried out by

Brown and others, however, suggest that this is not so.

2. Low flow rates of blood even with the metabolic protection of hypothermia may lead to inadequate oxygenation of some organs or tissues or to a spotty distribution of blood within any particular organ. Focal areas of necrosis have been reported by Sarajas and associates in the hearts of hypothermic dogs subjected to surgery. This matter requires considerable further study, but the gross metabolic pattern and the behavior of animals subjected to differential hypothermia by the method herein reported suggest that this is at least not very important.

3. Warming of blood may lead to liberation of oxygen bubbles since the affinity of blood for oxygen decreases as the temperature rises. Such liberation becomes more likely with the high oxygen tension commonly found in most oxygenator circuits. Until adequate control of the oxygen tension is possible, this is probably a real problem, and for this reason we have discontinued actual warming of the blood. No significant sacrifice in the flexibility or usefulness of the method has resulted.

4. Monitoring by use of the electroencephalogram has come to be a usual practice in heart-lung work, but with hypothermia such monitoring is probably less meaningful. Fortunately, the protection afforded by the hypothermia makes speed of detecting difficulties less important and electroencephalographic monitoring is probably therefore unnecessary.

5. Cardiac arrhythmias, especially ventricular fibrillation, have been associated with simple hypothermia and might be expected to constitute a problem in the method herein reported. Since potassium citrate arrest of the heart is generally employed and ventricular fibrillation is readily reversible, arrhythmias have not been a problem.

SUMMARY

Extracorporeal blood flows in the neighborhood of 25 per cent of the basal cardiac output result in hypoxia and metabolic acidosis when employed at normal temperatures. By cooling the blood just before returning it to the body, marked reduction in the temperature of the heart, brain, liver, and kidney can be produced easily with great economy in heat transfer, since the great bulk of the animal or patient, consisting of skin, muscle, and bone, is cooled much more slowly. The result is a marked oxygen saving, due to the direct antimetabolic effect of the cooling. Metabolic acidosis can be avoided and so far no irreversible effects of the cooling have been discoverable. Warming is so greatly facilitated by the heat stored in the nonvital areas that it is not necessary to warm the blood returning from the extracorporeal circuit. The use of safe low extracorporeal flows offers a number of possible advantages including great simplicity of cannulation and of the pump oxygenator design and operation. It is believed that human trial of this procedure is indicated.

REFERENCES

1. Boerema, I. A., Wildschut, A., Schmidt, W. J. H., and Broekhuysen, L. Experimental researches into hypothermia as an aide in the surgery of the heart. Arch. Clin. Neerl., 1951, 3: 25.
2. Brock, R. C., and Ross, D. N. Hypothermia—III, the clinical application of hypothermic techniques. Guy's Hosp. Rep., Lond., 1955, 104: 99.
3. Brown, D. E. S. Some considerations of physiochemical factors in hypothermia; the physiology of induced hypothermia. Pp. 1–7. Publication 451, National Academy of Sciences—National Research Council, Washington, D. C., 1956.
4. Dammann, J. F., and Muller, W. H., Jr. Problems in methods of inducing hypothermia by use of drugs and internal cooling; the physiology of induced hypothermia. Pp. 422–438. Publication 451, National Academy of Sciences—National Research Council, Washington, D. C., 1946.
5. Delorme, E. J. Hypothermia in dogs; technical report ONRL 83-53, Office of Naval Research, London, June 22, 1953.
6. Gollan, F. The physiology of induced hypothermia. P. 432. Publication 451, National Academy of Sciences—National Research Council, Washington, D. C., 1956.
7. Gollan F., Blos, P., and Schuman, H. Exclusion of heart and lungs from circulation in the hypothermic, closed-chest dog by means of a pump oxygenator. J. Appl. Physiol., 1952, 5: 180.
8. Peirce, E. C., II. The value of a low flow pump oxygenator combined with hypothermia. Tr. Am. Soc. Artif. Int. Organs, 1956, 2: 28.
9. Idem. Regulation of blood volume during partial and total cardiopulmonary by-pass. In press.

10. Peirce, E. C., II, and Polley, V. B. Differential hypothermia for intracardiac surgery; preliminary report of a pump oxygenator incorporating a heat exchanger. Arch. Surg., 1953, 67: 521.
11. Ripstein, C. B., Friedgood, C. E., and Solomon, N. A technique for the production of hypothermia. Surgery, 1954, 35: 98.
12. Sarajas, H. S. S., Senning, A., and Kaplan, J. Heart damage in dogs subjected to hypothermia, circulatory arrest, and cardiac surgery. Am. Heart J., 1956, 52: 836.
13. Sealy, W. C., Brown, I. W., Jr., Young, W. G., Jr., Stephen, C. R., Harris, J. S., and Merrit, D. Hypothermia; low flow extracorporeal circulation and controlled cardiac arrest for open heart surgery. Surg. Gyn. Obst., 1957, 104: 441.
14. Sealy, W. C., Young, W. G., Jr., Harris, J. S., and Merritt, D. H. Potassium, magnesium, prostigmine solution for induced cardiac arrest; laboratory and clinical observations on this method during extracorporeal circulation and hypothermia. Tr. Am. Soc. Artif. Int. Organs, 1957, 3: 19.

REGIONAL HEPARINIZATION AND HEPARIN INACTIVATION BY ERYTHROCYTES

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REGIONAL HEPARINIZATION is the administration of heparin into a vessel at a rate which prevents thrombosis in the heparinized vessel and its ramifications without elevating the clotting time of blood in the vascular system other than the vessels into which the heparin is injected. Murray and Best first described the concept of regional heparinization in 1938. However, they made no attempt to evaluate the actual regional effects of heparin. Freeman has used the procedure. In 1 case a slow intra-arterial injection of heparin into the left iliac artery was maintained for 3 days. A single clotting time determination showed a clotting time of 17 minutes in the left iliac vein while it was 7 minutes in the antecubital vein. Wylie and associates performed the first experiment designed to evaluate the effectiveness of regional heparinization. They performed 5 experiments on dogs and demonstrated that regional heparinization was clinically feasible.

However, prolonged regional heparinization of a large artery with blood flowing rapidly through it is often attended by general heparinization. This happens because the inactivation of heparin in the artery takes place more slowly than the circulation time of the blood through the extremity. Nonetheless, regional heparinization could be assuredly produced by neutralizing the heparin given intra-arterially before it enters the general circulation. This effect has been produced by Gordon and associates (3, 4) by infusing heparin into the femoral artery and protamine into the respective femoral vein.

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The experiments reported here were performed in order to test the feasibility of regional heparinization over a 5 hour period by employing varied infusion rates.

EXPERIMENTAL METHODS

Experiments were performed on healthy mongrel dogs as well as on animals that had been subjected to previous surgical procedures. Heparin sodium[1] diluted in 0.85 per cent saline was used in all experiments. The dogs were anesthetized with sodium pentothal which has been shown to have no effect on the clotting time of normal dogs.

The McCleery silicone tube method of measuring clotting time was used with slight modification.[2] Silicone (DC 200) was applied to all surfaces exposed to blood. Siliconized syringes were washed 3 times with saline before drawing blood samples.

The following technique gave the most reproducible results and was used in all our experiments: 6 cubic centimeters of bubble free blood were permitted to flow gently down the side of 13 by 100 millimeter silicone coated test tubes containing the 0.2 cubic centimeter of dextran. Tube No. 3 was filled first, tube No. 2 next, and tube No. 1 last. Tube No. 3 is gently tilted at 5 minute intervals until the end point is reached. This procedure is repeated in tubes Nos. 2 and 1. The end point is defined as the time when the sedimented red blood cell mass upon tipping the tube to a 45 degree angle flows slightly at the center but not at

[1]Heparin sodium, 1,000 units per cubic centimeter (1 unit = 1/130 mgm.).

[2]Two-tenths cubic centimeter of 6 per cent dextran was placed in the tubes before the blood was put in them. This small amount of dextran was used to accelerate the sedimentation rate of the erythrocytes effecting a clear interface between the plasma and red cell mass before the clot formed.

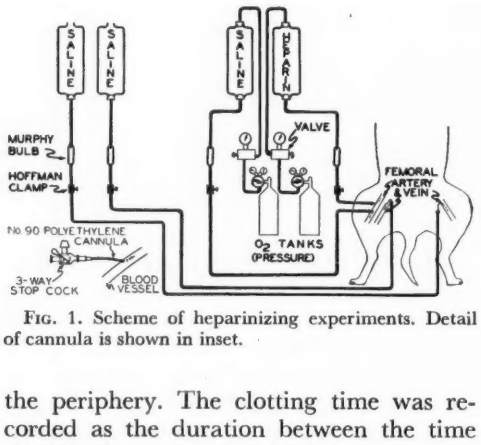

FIG. 1. Scheme of heparinizing experiments. Detail of cannula is shown in inset.

the periphery. The clotting time was recorded as the duration between the time the blood sample was drawn and the end point reached in tube No. 1. Reproducibility of results is best indicated on the graphs of experimental data.

To determine whether the required precision of infusion rates was attainable by our cannulation technique, the following experiments were performed. The jugular, carotid, and femoral vessels were cannulated. Infusions of 0.85 per cent saline at 120 drops per minute were administered into both arteries and veins of 5 normal dogs over 1½ hour periods. We found that the normal clotting time of about 30 minutes at

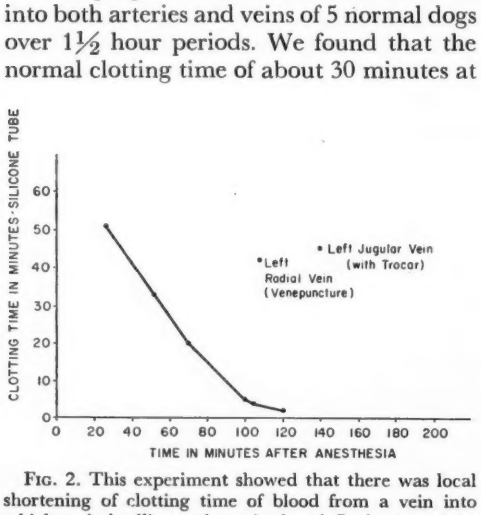

FIG. 2. This experiment showed that there was local shortening of clotting time of blood from a vein into which an indwelling catheter is placed. Reduction of the clotting time developed progressively over 104 minutes. That clotting time in the general circulation is not affected is indicated by normal clotting time of blood from the jugular and radial veins.

the beginning of the experiment gradually decreased to less than 1 minute. Invariably, while drawing the final sample, blood clotted as it was aspirated into the syringe. Such shortening of the clotting time attending a mere saline infusion seemed to have obvious clinical implication and warranted further investigation.

A dog was anesthetized with pentothal sodium and allowed to remain undisturbed on the operating table for 1 hour, at which time a silicone coated trocar was inserted into one jugular vein. After 67 minutes similar trocars were placed into the opposite jugular vein and the radial vein (Fig. 2). This experiment showed that there was local acceleration of blood clotting time from a vein into which an indwelling catheter is placed. Shortening of the clotting time of the general circulation is not effected. This phenomenon was noted in samples from all vessels during the control period of subsequent heparinizing experiments. Samuels' excellent study of endothelial changes attending varying degrees of trauma to blood vessels suggests an explanation for the localized hypercoagulability of blood around a venipuncture. He showed an aggregation of platelets, thrombin, and fibrin at the intercellular cement substance between endothelial cells when light digital pressure, sufficient only to approximate the intimal surface, was applied to a vein. More severe trauma was associated with accelerated aggregation of the clotting elements.

EXPERIMENTS WITH REGIONAL HEPARINIZATION

The heparinizing experiments utilized the femoral artery of one leg for heparin infusion. The heparin-saline solution was delivered from pressure reservoirs precisely regulated at 190 millimeters of mercury with flow rates controlled by Hoffman clamps and Murphy bulbs (Fig. 1). The heparin solution was infused via a No. 90 polyethylene catheter passed into the femoral artery just below the iliac artery and directed centrally against the blood stream.

No samples were drawn from this cannula. A similar cannula was inserted in the direction of the blood stream 2 centimeters distal to the heparinizing cannula in the femoral artery. Similar indwelling cannulas were placed in the femoral veins of both the heparinized and control legs. Uncontaminated blood specimens were obtained from each cannula by allowing a few drops of blood to reflux out of a three-way stopcock before collecting the sample. We attempted to reduce the inherent error in clotting time tests by using frequent samples drawn through indwelling cannulas (Fig. 1) and tested by the silicone tube method at controlled temperatures. Figures 2 to 9 are typical graphs of the results of 13 experiments in regional heparinization.

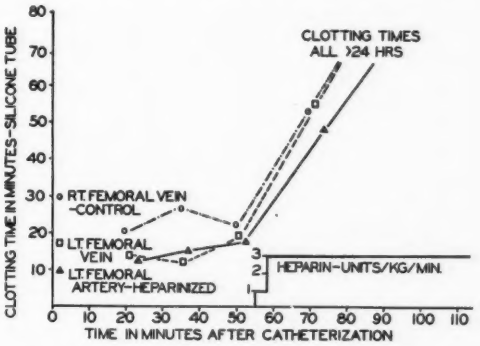

FIG. 3. Large doses of heparin were started after a 55 minute control period. Clotting times in all vessels shortened abruptly as indicated by the first sample taken 13 minutes after heparinization was begun. Heparin was infused for 75 minutes during which time samples were taken at 15 minute intervals. No regional effect is apparent as the clotting time in each of the three vessels become excessively prolonged and the curves become asymptotic with the ordinate. These data correlate well with work done by Jacques (5).

DISCUSSION

Pertinent principles used in our experiments are: (1) The silicone tube clotting time technique provides a more sensitive index of coagulation time than the more commonly used Lee-White method. (2) The blood samples were drawn from indwelling cannulas which method eliminates the tissue fluid contamination attending percutaneous blood sampling. (3) The experiments have been conducted over relatively long periods of time—from 3 to 6 hours. This is important because regional heparinization was first used on a hypothetical basis and later supported by experiments of 2 hours' duration.

It seems logical to us that any regional prolongation of the clotting time at the site of heparin infusion will be closely related to the rate of heparin inactivation by the blood or tissues near the site of infusion and the excretion of heparin from the general circulation of the animal. Assays of heparin from the tissues and blood show that even after injections of large amounts of heparin there was no significant change in the heparin content of the liver and lungs where heparin is usually found in highest concentrations. However, a substantial rise in the heparin concentration in the intestine was noticed after large intravenous infusions were given. Jacques (5) believed that the intestines had some role in heparin excretion although, paradoxically, no increase in heparin concentration was found in either the intestinal contents, feces, or urine. Further work by Jacques (6) implicates enzymatic inactivation of heparin by heparinase.

Because little work had been done on the absorption of heparin by the vessel wall itself, we compared histologic sections of the vessels into which the heparin was injected with the

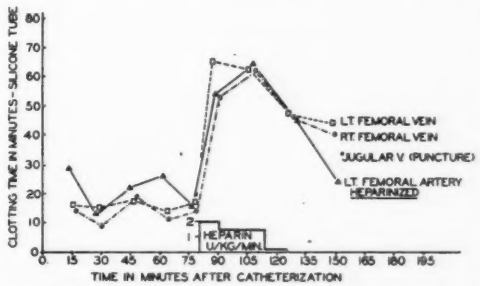

FIG. 4. Here the control period of 80 minutes was run and a baseline established before small doses of heparin were administered. The heparin was infused at rates indicated on the graph and within 1 hour the clotting time rose to 65 minutes in all vessels. It is clear from these data that no regional effect is present.

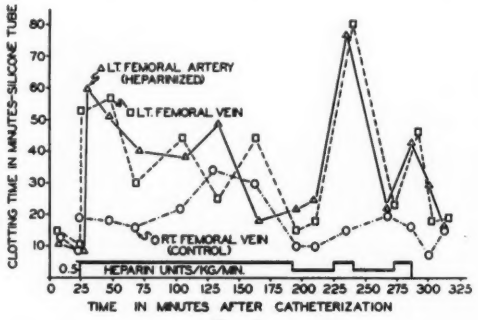

FIG. 5.

FIG. 5. Heparin was started at 1.0 unit per kilogram per minute after a 25 minute control period. For a short time there was significant prolongation of the clotting time in the blood from the heparinized limb compared to the blood from the opposite leg. However, this difference soon disappeared and subsequently samples taken from both legs showed no significant difference one from the other. The heparin infusion was then slowed to 0.25 unit per kilogram per minute for 35 minutes and then started again at 0.5 unit per kilogram per minute. Transient elevations in clotting time occurred in the heparinized limb which did not occur in the control limb. Upon continuance of the slow infusion the samples from both limbs attained practically identical clotting

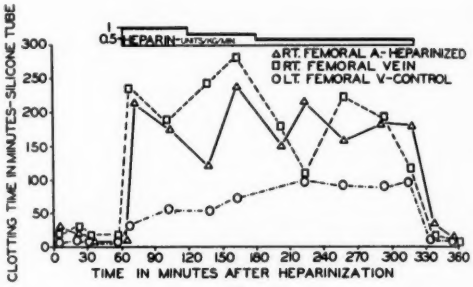

FIG .6.

FIG. 6. The animal used in this experiment underwent a similar operative procedure 2 days previously (Fig. 8). On exposure of the femoral vessels the left femoral vein was greatly thickened; it appeared gray and fibrotic. The right femoral vein was somewhat gray but was thinner and more turgid than the left. The arteries appeared normal. In the second experiment the heparin was administered into the artery that had not received it before. This was the only experiment in the series which showed a more than transient regional effect but even in this instance the trend was toward general heparinization.

controls into which saline had been infused. After fixing in basic lead acetate and formalin, these sections were studied with phase-contrast microscopy before staining. Alternate serial sections were stained with toluidine blue. Neither the stained nor the unstained sections showed mucopolysaccaride precipitation or metachromatic staining suggestive of heparin absorption in either the heparinized or control vessel.

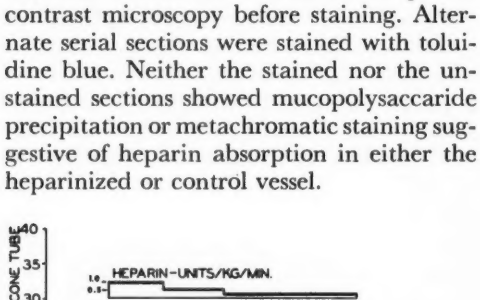

FIG. 7. Data from 4 experiments were integrated to demonstrate graphically the gradual equilibration of clotting time in the local and systemic circulations.

A decrease in serum calcium concentration associated with heparinization was noted by Van Bergen and confirmed in our own in vitro studies. The possibility of heparin absorption by the red blood cells was entertained by Chargoff and Olson who found that the clotting time value of heparinized plasma tends to return to normal more rapidly than does the clotting time of heparinized whole blood. By contrast, Von Kaulla and Henkel found that after heparinization there was a shorter clotting time in citrated whole blood than in citrated plasma. In investigating this phenomenon Von Kaulla and Henkel exposed human erythrocytes to calcium chloride-heparin mixtures for varying lengths of time. They then reconstituted the blood with citrated plasma and discovered that the clotting time varied inversely with the exposure time of the red blood cells to the heparin-calcium chloride solution. This indicated that the inactivation of heparin varies directly with its exposure time to the erythrocyte. They believed that heparin may have been adsorbed by the red blood cells.

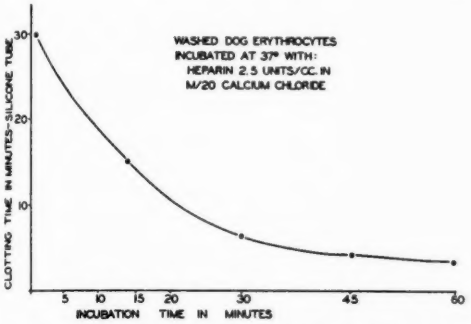

FIG. 8. The inactivation of heparin by washed dog erythrocytes.

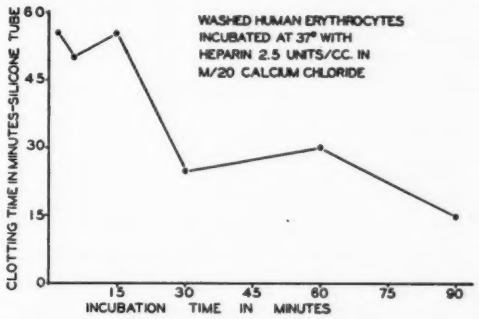

FIG. 9. The inactivation of heparin by washed human erythrocytes.

Another observation pertinent to the problem of how heparin is inactivated is that of Jacques (5) who found enhancement of the dog's ability to inactivate heparin as the rate of heparin administration was accelerated up to a maximum of 2 units per kilogram per minute.

In brief any regional effect of heparinization will be affected by at least three factors: (1) the rate of infusion, (2) the rate of inactivation of heparin in the blood, and (3) the circulation time of blood in the area.

Assuming that the circulation time through a given extremity is 1 minute and the maximum rate of heparin inactivation within the circulation of the extremity is 2 units per kilogram per minute, the continuous arterial infusion of heparin at a rate of 1 unit per kilogram per minute should be attended by regional heparinization because the heparin given is being inactivated within the tissues of the extremity as fast as it is being administered.

INACTIVATION OF HEPARIN

After the first experiments had demonstrated our incapacity to effect regional heparinization except for brief periods of time, in vitro experiments were devised in the attempt to elucidate the role of the red blood cell in the inactivation of heparin. The heparin first used in the experiments was of the same manufacture and stock used in the regional heparinization studies; in later experiments crystalline heparin sodium was used.

EXPERIMENTAL METHODS

Freshly drawn venous blood was citrated immediately in tenth-molar sodium citrate. The plasma fraction was removed by centrifugation and decantation. The erythrocytes were then washed 6 times with saline and then packed to a concentration of 10,000,000 cells per cubic millimeter. The packed cells were then incubated at 37.5 degrees C. with equal parts of heparin-calcium chloride solution. The heparin concentration was 2.64 units per cubic centimeter and the calcium chloride was twentieth molar. After varying lengths of incubation time from 1 minute to 2 hours, equal volumes of plasma were added to the heparin-calcium chloride-red blood cell mixture. The clotting times of the samples showed a decrease in clotting time that was related to incubation time in a somewhat logarithmic fashion (Fig. 8). Controls of calcium chloride-red blood cells without heparin did not affect the clotting time of samples added to plasma after similar periods of incubation. These data suggest that heparin is inactivated or bound by the washed erythrocyte. Calcium concentration of the heparin-calcium chloride-red blood cell mixture was noted to decrease while the heparin-calcium chloride solution was incubated with red blood cells. The lowest calcium concentration was 7.6 milliequivalents per liter noted at the end of the experiment when the clotting time had returned to normal. The *p*H of the erythrocyte-heparin-calcium chloride mixture re-

mained constant throughout the experiments. There was no change in the catelectrophoretic migration rates of the incubated and heparinized erythrocytes.

DISCUSSION

These experiments show that the erythrocyte is capable of inactivating heparin in vitro, and if it possesses this capacity in vivo it may well be a very important factor in the in vivo inactivation of heparin, in addition to the serum enzymatic destruction of heparin. Whether this phenomenon is related to destruction of the heparin by an intracellular enzyme, the binding of heparin to the red blood cells or some other action is unknown.

SUMMARY

1. Regional heparinization can be obtained only transiently even with slow rates of intra-arterial injection; general heparinization ultimately occurs.

2. Washed human erythrocytes inactivate heparin in vitro.

3. The clotting time of blood taken from vessels into which cannulas or needles have been placed is remarkably shortened.

REFERENCES

1. Chargoff, E., and Olson, K. B. The chemistry of blood coagulation—VI, studies on the action of heparin and other anticoagulants, the influence of protamine on the anticoagulant effect in vivo. J. Biol. Chem., 1937, 122: 153.
2. Freeman, N. Regional heparinization in vascular surgery. Surg. Gyn. Obst., 1950, 90: 406–412.
3. Gordon, L. A., Richards, V., and Perkins, H. A. Studies in regional heparinization—I, the use of simultaneous neutralization with protamine; preliminary studies. N. England J. M., 1956, 255: 1025.
4. Gordon, L. A., Simon, E. R., Rukes, J. M., Richards, V., and Perkins, H. A. Studies in regional heparinization—II, artificial kidney hemodyalysis without systemic heparinization; preliminary report of a method using simultaneous infusion of heparin and protamine. N. England J. M., 1956, 255: 1063.
5. Jacques, L. B. The effect of intravenous injections of heparin in the dog. Am. J. Physiol., 1939, 125: 98.
6. Idem. Heparinase. J. Biol. Chem., 1940, 133: 445.
7. McCleery, R. S., Yardborough, J. R., and Weidner, M. G. Silicone-tube coagulation time in phlebothrombosis. Surgery, 1952, 31: 28.
8. Murray, G. W. G., and Best, C. H. Use of heparin in thrombosis. Ann. Surg., 1938, 108: 163.
9. Samuels, P. B., and Webster, D. R. Venous endothelium in the inception of thrombosis. Am. Surg. Ass., 1952, 70: 126.
10. Van Bergen, T. M., and Hill, R. M. Effect of added heparin on calcium determinations in blood plasma. J. Laborat. Clin. M., 1937, 22: 862.
11. Von Kaulla, K. N., and Henkel, W. Heparin Adsorption durch Erythrocyten. Schweiz. med. Wschr., 1952, 82: 1128.
12. Wylie, E. J., Gardner, R. E., Johansen, R., and McCorckle, H. T. Experimental study of regional heparinization. Surgery, 1950, 28: 29.

OBSERVATIONS ON ARTHROPLASTY OF THE KNEE

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TREATMENT is often required to preserve or to regain function in the knee joint in the presence of chronic arthritis. The knee joint is attacked more frequently and more severely by rheumatoid arthritis than is any other articulation. If weight bearing is continued when active arthritis is present severe deformity or a stiff knee joint is often the end result. This severe damage can be prevented by early treatment, but the majority of patients fail to use measures for protection of the joint or the limitation of activity until the disease becomes less active. Many procedures have been advocated to relieve pain and to permit walking after the knee joint has been destroyed. These procedures can be divided into two groups: (1) those which protect the knee and prevent movement, e.g., rigid bracing of the knee or a stiffening type of operation which prevents motion permanently, and (2) operations by which an attempt is made to remove the cause of pain and permit motion by removing incongruities of the articular surfaces, thickened soft tissues, and ankyloses, e.g., plastic procedures and arthroplasty. The great majority of patients with irreparable damage to the knee joint prefer the second type of procedure, a knee joint in which the cause of the pain has been removed and which still possesses motion. This is usually the procedure of choice because there is usually severe restriction of motion in many other joints when chronic arthritis is present.

When a greatly deformed or stiffened knee joint is reshaped to permit motion and to avoid pain, a large bleeding, bony surface remains both over the femoral condyles and upon the articular surface of the tibia. It has been the experience of many surgeons that when these surfaces are left in contact, adhesions form quickly and the knee joint again stiffens. To prevent such stiffening after reshaping the articular surfaces, many materials have been interposed between the raw surfaces—fascia, animal membranes, metals, and plastics. Fascia has been used most commonly, but in arthritis it is a defective membrane and wears through very quickly permitting adhesions and ankylosis. For this reason, fascia has been most disappointing in our hands. Metals and animal membrane have been little better. In 1942 we began experimenting with plastic membranes in place of fascia. Nylon membrane, .003 inch thick, was found to be most satisfactory for covering these raw surfaces. Our first patients were operated upon in 1944. The present article is a report of our experience with 100 arthroplasties of the knee with the use of nylon membrane. All of these patients have been followed up for 2 years or longer after operation. Twenty more recent operations are not in this study.

This procedure is considered for the relief of severe pain, extremely limited motion, or ankylosis. Stiffness or limitation of motion in one knee usually is not a serious handicap; but involvement of one knee joint only is rarely encountered in chronic arthritis. Arthritis usually produces restriction of motion in many joints of the body. Arthroplasty is never performed when active arthritis is known to be present. It is performed only in the absence of infection or tumor. In osteoarthritis, arthroplasty is employed only when the correction of articular incongruities leave large raw areas on the articular surfaces. If these areas are larger than 2 square inches then nylon membrane is used for stiffness in the knees, a fairly

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TABLE I.—POSTOPERATIVE FUNCTION OF KNEE JOINT

Pain		*Instability*		*Active motion*		*Flexion deformity*		*Valgus*		*Aid on walking*	
None	70	None	91	Normal	9	None	88	None	88	None	18
Slight	21	Slight	6	70° to 90°	50	5° to 10°	9	5°	5	Cane part time	45
Moderate	7	Moderate	2	40° to 70°	31	10° to 20°	3	10°	6	Crutches	36
Severe	2	Severe	1	40°	10	20°	0	30°	1	Not walking	1

common sequel to Still's disease. Arthroplasty is considered during adolescence only after growth is completed.

The technique employed has been simplified somewhat from our original description (1). The knee joint is exposed through a long parapatellar incision. If the knee joint is ankylosed it must be opened by an osteotome through the previous joint plane. If the knee can be flexed 40 degrees or more, the patella is reflected laterally. If the knee cannot be flexed this amount the quadriceps tendon should be lengthened and the patella is reflected downward. This procedure makes the further dissection about the knee much easier. About ½ inch is removed from the distal end of the femoral condyles depending upon the irregularity of the articular surfaces. The collateral ligaments are not disturbed. The femoral condyles are reshaped into a shallow wedge. The upper end of the tibia is modeled into a shallow trough to fit the femoral surfaces. Nylon membrane is then fitted over the reshaped lower end of the femur. After closure of the wound the entire leg is encased in plaster with the knee extended. Exercises are begun in 10 days. Walking with partial weight bearing is started in 3 weeks. Exercises are gradually increased in vigor. Usually in 9 to 18 months there is good function and normal strength.

One hundred arthroplasties were performed upon 86 patients in this study. The age of the patients varied from 17 to 71 years. Three-fourths of them were more than 30 years old. The oldest patient is now 76 years of age with good, painless function in the knee joint. Bony ankylosis resulting from rheumatoid arthritis was present in 20 knees. In 62 knees there was destruction of the knee joint with articular incongruity, deformity, and limited, painful motion. Seven patients had osteoarthritis with articular disalignment and severe pain. Eleven patients had traumatic arthritis with destruction of the articular surfaces and severe deformity, 5 with bony ankylosis and 3 the result of gunshot wounds.

The postoperative function is given in Table I. Pain and stability were measured from none to severe. Active motion was measured in degrees as was valgus deformity at the knee. Walking was recorded as: without support, with occasional cane, with constant cane or crutch, inability to walk. Seventy of these patients had no pain in the knee: 21 had slight pain on weight bearing; 7 had moderate pain on weight bearing; 2 had pain both on weight bearing and at rest. None required opiates. Tests for lateral and anteroposterior stability were made upon all patients. In 91 there was no lateral or other instability. Six patients had slight, less than 10 degrees of lateral instability. Two patients had from 10 to 15 degrees of lateral movement, and 1 had 25 degrees of lateral instability.

All of these patients had ankylosis or very limited motion in the knee before operation. After operation there was no limitation of the normal range of motion in 9 knees. There was active flexion from full extension of from 70 to 90 degrees in 50. Motion in flexion of from 40 to 70 degrees was found in 31. Less than 40 degrees of motion in flexion were found in 10, in 6 of which fibrous or bony ankylosis had taken place. All knee joints were splinted in full extension after operation. While most of the patients regained adequate strength in the quadriceps muscle, a number soon discontinued exercises and the extensor muscles remained weak. In these patients a flexion deformity gradually appeared. There was no flexion deformity in 88 knees. In 9

flexion deformity of 5 to 10 degrees was present and in 3 the flexion deformity was of 10 to 20 degrees. Flexion deformity was not greater than 20 degrees in any instance.

A valgus deformity is prone to develop whenever there is osteoporosis in the bones. This was observed in varying degree in 12 patients. It was less than 5 degrees in 5 patients; from 5 to 10 degrees in 6, and 30 degrees in 1. In this latter case a corrective femoral osteotomy was required. All patients except 1 are walking on the operated upon knees. Eighteen are walking without support. Forty-five are using a cane part time. A cane or crutches are used for all walking by 36. The 1 patient not walking had a severe exacerbation of rheumatoid arthritis 6 years after operation and is now confined to a wheelchair.

Some type of employment was followed after arthroplasty by 74 patients who had had 86 operations of the knee. In 44 it was the same work as before. In the others sitting work was the type of employment. Twelve patients (with 14 involved knees) were not working. The operation in no instance was the cause of the unemployment. Inability to work was due to active arthritis or to the disabilities which it had produced. More persistent attempts at rehabilitation carried out during the last few years have shown that most of these disabled patients can be trained or retrained for jobs within their physical limitations.

From these data we attempted to grade the end results. We called the result excellent when there was no pain on motion, active motion of 90 degrees or greater, normal stability, and the ability to walk without support. There were 9 in this group. In a good result there was no pain or very mild pain on weight bearing movement of from 70 to 90 degrees, normal stability and walking without support, or with a cane occasionally for long distances. There were 50 in this category. In a fair result there was slight pain on motion, a range of active motion of between 40 and 70 degrees, normal stability, and walking with a cane.

TABLE II.—BILATERAL NYLON KNEE OPERATIONS UPON 14 PATIENTS

	No. of cases
Diagnosis	
Rheumatoid with destruction of joint	10
Rheumatoid ankylosed	4
Function	
Excellent	1
Good	8
Fair	5
Poor	0
Failure	0
Reoperations	
Removal of nylon: Bilateral	3
Unilateral	2

Thirty-one operations were in this group. A poor result was one in which there was pain on motion or at rest, a range of active motion of less than 40 degrees, slight instability, support of cane or crutches in walking, and support to the knee. There were 10 in this group.

There were 14 patients with arthroplasties on both knees (Table II). In these patients an operation on the other knee was carried out at the patient's request in from 1 to 3 years after the first operation. All of these were patients with severe rheumatoid arthritis, 4 of them with bilateral ankylosis. Only 3 of them could walk preoperatively. These patients were no more difficult to care for and the end results were similar to those obtained in patients who had the operation on on one knee only. However, we now believe that for individuals who are engaged in strenuous work it is better and a more durable end result is achieved if the operation is performed on one knee and arthrodesis on the other in a good position for function All but 1 of this group of patients are working. There were no poor results in this group. The nylon was removed for locking in 8 knees. The function was undisturbed whether the nylon was removed or not.

In 30 cases, further surgical procedures were required after the arthroplasties (Table III). In 11 instances, manipulation under anesthesia was performed to increase the range of flexion, to stretch postoperative adhesions in 5 and because of persistent contracture of the extensors of the knee in 6, the severity of which was not appreciated at the original operation. Operative lengthening

TABLE III.—SUBSEQUENT OPERATIONS

Type of surgery and condition present	*No. of knees*
Manipulation	11
Postoperative adhesions	7
Contracture of quadriceps	4
Removal of nylon	15
Torn	6
Pain with locking	2
Injury	4
Infection	3
Quadriceps lengthening	2
Tight muscle	2
Femoral osteotomy	1
Valgus knee	1
Leg amputation	1
Tendon slough	1

of the quadriceps tendon can be carried out most easily at the time of arthroplasty. The nylon membrane was removed from 15 knees within periods varying from 4 months to 7 years after the original operation. The causes for the removal of the nylon were: tearing loose from its sutures to the femur in 6 cases, a wearing through with subsequent rolling of the edge and impingement or locking of the articular surfaces in 2, infection in 3, and subsequent injury to the knee requiring arthrotomy in 4 cases. In no case was the nylon removed for sensitivity to the nylon itself or from extensive foreign body reaction, both of which have been mentioned by Waldius as theoretic objections to the use of nylon membrane. The quadriceps tendon in 2 knees was lengthened to increase flexion. A femoral osteotomy was performed in 1 knee for a severe valgus deformity. This deformity occurs when the bone is osteoporotic or cystic changes are present near the articular surface. In 1 patient with a postoperative slough and necrosis of patellar tendon, amputation rather than arthrodesis was done at the patient's insistence.

These secondary operations gave us an opportunity to observe the changes in the knee joints after arthroplasty. On opening the knee joint a firm fibrous tissue was seen beneath the nylon membrane. This was observed as early as 16 weeks after operation. It provided a smooth gliding surface for articular function. No formation of fibrocartilage or hyaline cartilage was seen. Fluid from these joints was normal synovial fluid. In none of these knees did the removal of the nylon decrease the range of motion or interfere with subsequent function. In reoperations 3 or more years after arthroplasty and in 2 cases observed at autopsy, fraying or erosion of the nylon was found on the weight bearing surface. The erosion of the nylon in these patients had caused no symptoms and had not disturbed function. The question has been raised as to whether it would not be better to remove the nylon after firm fibrous tissue had formed beneath it. However, the patients are usually comfortable and happy to have motion and will not consent.

SUMMARY

1. Nylon membrane is an effective material for interposition in arthroplasty of the knee joint in chronic arthritis.

2. The indications for arthroplasty of the arthritic knee joint are severe pain and great restriction of motion when both knees and other joints are seriously involved.

3. Satisfactory function as shown by lack of pain, a good range of active motion, normal stability, and the ability to walk without support was shown by three-fourths of the patients 2 years after operation.

4. In the 14 instances of bilateral arthroplasties, function was as good as that resulting from unilateral arthroplasties. However, we now believe that greater endurance and stability will result if arthroplasty is performed on one knee joint only and a rigid brace or an arthrodesing operation is employed on the other side.

5. Secondary operations were required in 30 cases. We believe that the quadriceps muscle should be lengthened to secure flexion whenever the knee joint has been fixed in extension for more than 1 year before operation. The nylon membrane wears away on weight bearing surfaces after 3 years. Its removal in 15 knees has not disturbed function in these knee joints.

REFERENCES

1. Kuhns, J. G., and Potter, T. A. Nylon arthroplasty in rheumatoid and osteoarthritis. Am. Rheumat. Dis., 1950, 10: 22.
2. Waldius, B. Arthroplasty of the knee using an endoprosthesis. Acta orthop. scand., 1957, suppl. 24.

PROLONGED HYPOTHERMIA IN EXPERIMENTAL PNEUMOCOCCAL PERITONITIS

II. Survival of Hypothermic Animals and Effect of Combined Hypothermia and Antibiotics

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IN A PREVIOUS PUBLICATION (2) the effects of prolonged hypothermia on the length of survival of mice given lethal peritonitis with pneumococcal III have been described. The hypothermic animals were found to survive significantly longer than the normothermic controls. The purpose of this study is to compare long term survival under similar laboratory conditions using an inoculum adjusted to approximate 50 per cent control survival, and to study the effect of combining hypothermia with partially protective doses of penicillin.

MATERIALS AND METHODS

Five hundred sixty-one 6 to 8 week old female Webster strain white mice were used in this study, as summarized in Table I. Two hundred forty-five of these animals were used in determining the differences in long time survival between 103 hypothermic animals and 142 normothermic controls. One hundred seventy-eight mice were used in the 1 injection and 138 animals in the 2 injection studies.

Inoculum. Diplococcus pneumoniae III was maintained by growth on blood agar and standard virulence maintained by weekly subcultures. The inoculum was prepared by picking at random 3 colonies from the stock agar plate, transferring these to a 20 by 150 millimeter culture tube containing 20 milliliters of trypticase soy broth, and incubating at 37 degrees C. for 18 hours. Intraperitoneal injection of 0.5 milliliter of a 10^{-5} dilution of this culture was found to approximate a median lethal dose. Having established the virulence of this culture, it was preserved at −10 degrees C. and was used for both experimental and control runs. This technique of inoculum preparation was found to give more consistent results than that employed in the previous study (2).

In vitro growth studies were accomplished using 5 milliliters of a 10^{-5} dilution of Diplococcus pneumoniae type III prepared as described, and the turbidity of the culture tubes measured at hourly intervals on a Beckman spectrophotometer set at a wave length of 540 microns. Organisms incubated at 37 degrees were compared with those grown at 22 degrees C.

Anesthesia and production of hypothermia. In order to attain generalized body hypothermia rather than mere chilling during exposure to cold, all hypothermic animals were narcotized by the following method. Two hours following intraperitoneal inoculation of the organisms 120 milligrams per kilogram of body weight of pentobarbital sodium were injected subcutaneously. When narcosis was established the animals were placed on an aluminum tray and transferred to a cold room at 4 degrees C. for 7 minutes, after

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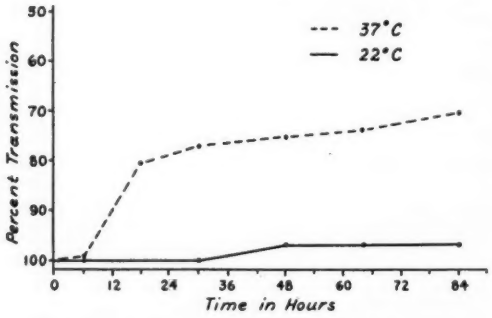

FIG. 1. Effect of cold on in vitro growth of Diplococcus pneumoniae type III at 10^{-6} dilution at 37 and 22 degrees.

which they were placed in a constant temperature box at 19 degrees C. for 24 hours. Anesthesia was maintained by injections of 100 milligrams per kilogram of body weight of phenobarbital sodium 3 hours after initial administration of pentobarbital. Infrequently an additional injection of phenobarbital, 0.03 milligram per kilogram of body weight, was necessary during the hypothermic period to maintain adequate narcosis.

Body temperatures were recorded in previous experiments (2) and in representative animals in this study by the rectal insertion of plastic covered No. 24 constantan wire thermocouples with temperatures recorded on a Brown potentiometer.

Rewarming. Following 24 hours of hypothermia the animals were removed from the constant temperature box, placed in glass jars containing sawdust, and allowed to recover from the effects of hypothermia and anesthesia at room temperature. Characteristically, the animals awoke and walked about the cage within 1½ hours, and thereafter were observed for a 10 day period in a constant temperature (20 to 22 degrees C.) small animal room.

Confirmation as to cause of death. Postmortem examination was performed on each animal that died. In 36 animals in the early part of this study Wright's stain smears of peritoneal fluid were examined and an overwhelming pneumococcal peritonitis was confirmed. Similar studies in hypothermic animals without infection revealed far less peritoneal fluid and no bacterial organisms.

Antibiotic administration. Single injection.—Two hours following intraperitoneal infection with pneumococcus the animals of each experimental group were arbitrarily divided, one-half remaining normothermic and the remainder made hypothermic. Half of the normothermic and half of the hypothermic animals then were given 400 units of crystalline sodium penicillin G subcutaneously in 0.25 milliliter of water. The antibiotic was thus administered to the hypothermic animals just as cooling began.

Two injection studies.—Hypothermia might assert a beneficial effect on an infected animal given a subcutaneous antibiotic merely by delaying absorption and excretion of the antibiotic and thereby prolonging its action. In order to minimize this difference between the normothermic and hypothermic animals, a series of experiments was per-

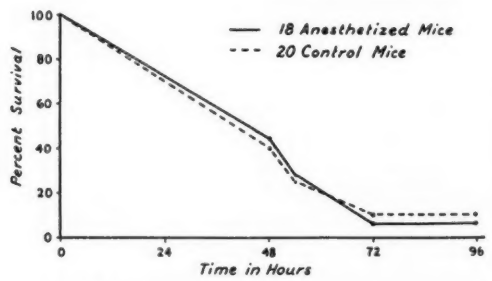

FIG. 2. Effect of anesthesia alone on survival of infected normothermic mice compared with controls.

TABLE I.—SUMMARY OF ANIMALS USED IN THIS STUDY

		No.
Long term survival study		245
Normothermic animals	142	
Hypothermic animals	103	
One injection penicillin (2 hours postinfection)		178
Normothermia alone	43	
Hypothermia alone	45	
Normothermia and chemotherapy	43	
Hypothermia and chemotherapy	47	
Two injection penicillin (2 and 14 hours postinfection)		138
Normothermia alone	31	
Hypothermia alone	37	
Normothermia and chemotherapy	31	
Hypothermia and chemotherapy	39	
Total		561

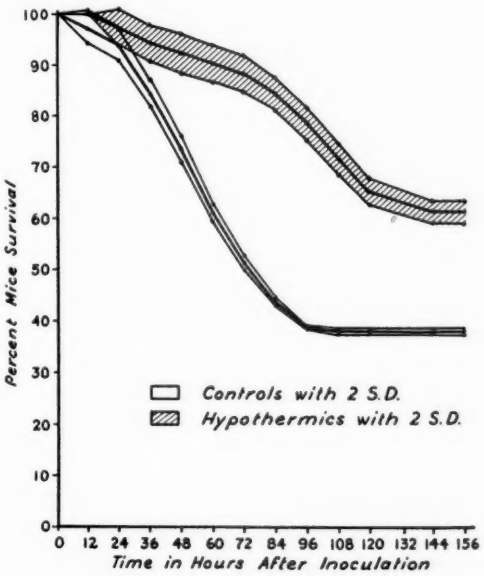

FIG. 3. Effect of hypothermia on survival of mice following a median lethal inoculation of pneumococci (excluding anesthesia deaths).

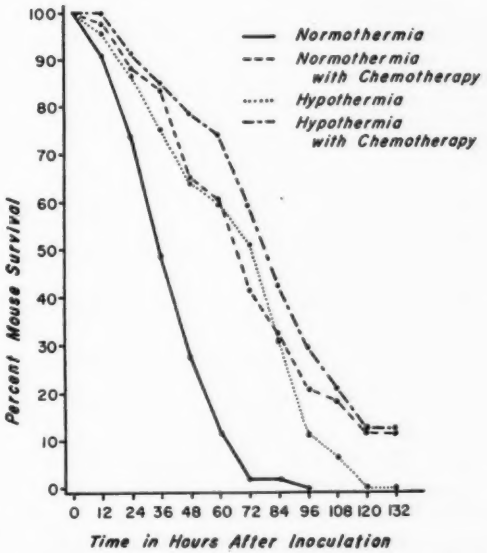

FIG. 4. Mouse survival following experimental pneumococcal peritonitis after 1 dose of penicillin given at onset of cooling compared to controls.

formed in which a second dose of 400 units of penicillin was given 12 hours following the first to both the normothermic and hypothermic animals receiving antibiotic therapy. Thus a more consistent elevation of antibiotic blood concentration was maintained in the normothermic animal similar to what might occur in the hypothermic animal if penicillin absorption and excretion were delayed.

RESULTS

A comparison of the rate of in vitro growth at 37 and 22 degrees C. is shown in Figure 1. It is evident that cold reduces the rate of bacterial growth in all phases.

Figure 2 compares survival of anesthetized infected normothermic animals (18 mice) with unanesthetized normothermic infected controls (20 mice). It is evident that anesthesia does not alter the response to infection.

Table II and Figure 3 show the effect of hypothermia on survival following a median lethal inoculation of pneumococci III in 103 hypothermic mice as compared with 142 normothermic control animals. Mean survival in the hypothermic group was 62 per cent compared to 38 per cent survival in the normothermic controls. This result

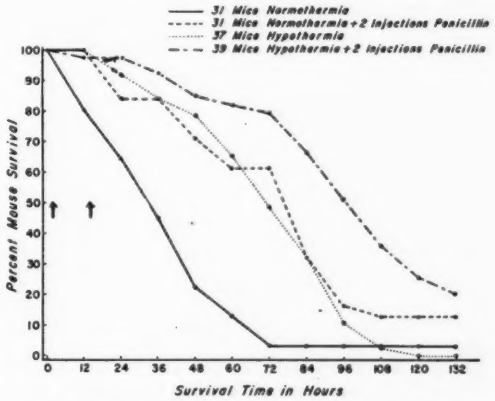
31 Mice Normothermia
31 Mice Normothermia + 2 Injections Penicillin
37 Mice Hypothermia
39 Mice Hypothermia + 2 Injections Penicillin
Percent Mouse Survival
Survival Time in Hours

FIG. 5. Survival following 2 doses of penicillin, one at onset of cooling, the other 12 hours later, compared with controls.

TABLE II.—EFFECT OF HYPOTHERMIA ON SURVIVAL FOLLOWING EXPERIMENTAL PERITONITIS (ANESTHESIA DEATHS EXCLUDED)

Experiment No.	*12 hours* H	*12 hours* C	*24 hours* H	*24 hours* C	*36 hours* H	*36 hours* C	*48 hours* H	*48 hours* C	*60 hours* H	*60 hours* C	*72 hours* H	*72 hours* C	*84 hours* H	*84 hours* C	*96 hours* H	*96 hours* C	*108 hours* H	*108 hours* C	*120 hours* H	*120 hours* C	*144 hours* H	*144 hours* C	*156 hours* H	*156 hours* C	*178 hours* H	*178 hours* C	*Deaths in hypothermic period*
15(13H & 20C)	13	20	13	20	11	13	10	6	10	5	9	5	8	5	7	5	6	5	6	5	6	5	6	5	6	5	7
16(15H & 20C)	15	20	15	20	15	20	15	18	15	12	15	7	14	6	13	6	12	6	11	6	9	6	9	6	9	6	5
17(12H & 13C)	12	13	12	13	12	13	12	12	12	9	12	7	11	6	10	6	10	6	9	6	9	6	9	6	9	6	3
18(18H & 20C)	18	18	17	16	17	13	17	11	16	9	16	7	15	6	15	4	13	3	12	3	11	3	11	3	11	3	2
20(10H & 14C)	10	13	10	13	10	12	10	11	10	11	10	10	10	8	10	6	9	6	5	6	5	6	5	6	5	6	5
21(11H & 20C)	11	19	10	17	9	15	8	14	8	12	7	11	7	7	6	6	6	6	6	6	6	6	6	6	6	6	9
23(6H & 10C)	6	10	6	9	6	9	6	9	6	8	6	8	6	7	6	7	6	7	6	7	6	7	6	7	6	7	4
24(12H & 15C)	12	15	11	15	11	15	11	14	10	11	10	9	10	8	8	7	7	7	7	7	6	7	6	7	6	7	8
25(6H & 10C)	6	10	6	10	6	10	6	10	6	10	6	9	6	9	6	8	5	8	5	8	5	8	5	8	5	8	14
																											Total 57 (due to causes other than pneumococcal peritonitis)
Total No. dead	0	4	3	9	6	22	8	37	10	55	12	69	16	80	22	87	29	88	36	88	40	88	40	88	40	88	
Total No. living	103	138	100	133	97	120	95	105	93	87	91	73	87	62	81	55	74	54	67	54	63	54	63	54	63	54	
Standard deviation	3.86	4.06	3.69	3.93	3.66	3.20	3.75	3.43	3.54	2.23	3.64	1.84	3.28	1.27	3.28	1.16	2.90	1.41	2.60	1.41	2.12	1.41	2.12	1.41	2.12	1.41	
X^2		4.96		1.15		4.60		12.13		24.33		35.16		40.02		36.90		26.02		16.37		11.90		11.90		11.90	
P		>.10		<.50		.10		<.001		<.001		<.001		<.001		<.001		<.001		<.001		<.001		<.001		<.001	

represents a protective effect of 24 per cent afforded by hypothermia. A total of 57 mice were lost during the 24 hour anesthetic period from causes other than pneumococcal peritonitis, and in every case an autopsy was performed to ascertain that the animal had not died of peritonitis. In most instances the cause of death, such as an overdose of anesthesia, or drowning in the water of the constant temperature box (Exp. 25, Table II) was immediately evident. These animals which had been proved to die from causes other than pneumococcal peritonitis are excluded from the data presented.

Figure 4 and Table III illustrate the effect of hypothermia combined with 1 injection of penicillin on the survival of 47 animals given 400 units of penicillin at the onset of hypothermia compared to 3 control groups: untreated normothermic controls (N); hypothermic animals not given antibiotics (H); and to animals given similar doses of penicillin but maintained at normal body temperature (NRx). It is evident that hypothermia prolongs survival, as was previously demonstrated (2). The dose of penicillin chosen was more protective (13.1 per cent survival) than hypothermia (no survivals). Of greatest importance was the fact that combining the two agents produced no greater survival (15 per cent) than did penicillin alone (13 per cent). The difference between these survival rates was not significant ($p = > 0.90$). Under these experimental conditions hypothermia added nothing to the therapeutic effect of penicillin when the two agents were combined.

The effect of combining 2 injections of 400 units of penicillin 12 hours apart with hypothermia is illustrated in Table IV and Figure 5. Comparison is again made with 3 simultaneous control groups: hypothermia alone (H); normothermia alone (N); and normothermia with chemotherapy (NRx). These studies can be summarized as follows: (1) hypothermia prolonged survival compared to the normothermic group; (2) hypothermia plus chemotherapy is but slightly more protective (26 per cent survival) than

TABLE III.—SURVIVAL FOLLOWING EXPERIMENTAL PERITONITIS IN HYPOTHERMIC ANIMALS TREATED WITH 1 INJECTION OF PENICILLIN COM-

TABLE III.—SURVIVAL FOLLOWING EXPERIMENTAL PERITONITIS IN HYPOTHERMIC ANIMALS TREATED WITH 1 INJECTION OF PENICILLIN COMPARED TO THREE GROUPS OF CONTROLS

	0 hours				12 hours				24 hours				36 hours				48 hours				60 hours			
Exp. No.	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*
1	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4	5	5	5	1	5	5	5
2	5	5	6	6	5	5	5	6	4	4	3	5	1	3	2	4	1	2	0	3	1	2	0	3
3	5	5	3	7	5	5	3	7	4	4	2	6	0	4	1	6	0	3	0	5	0	3	0	4
4	5	5	8	6	4	5	7	6	3	5	7	6	2	5	6	6	1	4	5	6	0	4	5	6
5	8	8	5	2	7	8	5	2	5	8	5	2	4	8	5	2	2	7	4	2	1	6	4	2
6	5	5	7	7	4	5	7	7	3	4	6	6	2	4	5	5	0	3	5	5	0	3	4	4
7	5	5	9	8	5	5	9	8	5	5	9	8	5	5	8	7	4	3	8	7	2	2	7	1
8	5	5	2	6	4	4	2	6	3	3	2	5	2	2	2	5	0	1	2	4	0	1	2	4
Total dead	0	0	0	0	4	1	2	0	11	5	6	4	22	7	11	7	31	15	16	10	38	17	18	12
Total living	43	43	45	47	39	42	43	47	32	38	39	43	21	36	34	40	12	28	29	37	5	26	27	35
Standard deviation	1.06	1.06	2.38	1.81	0.99	1.16	2.26	1.81	0.93	1.16	2.53	1.88	1.84	1.49	2.48	1.51	1.69	1.85	2.77	1.59	0.74	1.56	2.50	1.60
X^2	0		0		1.91		2.13		2.76		0.55		1.17		1.33		11.96		2.31		22.43		2.18	
P					>0.1		>0.1		.01		0.5		<0.3		>0.2		<0.01		>0.1		<0.01		>0.1	

	72 hours				84 hours				96 hours				108 hours				120 hours				132 hours			
Exp. No.	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*
1	0	4	5	5	0	3	4	5	0	3	3	5	0	3	2	5	0	3	0	4	0	3	0	4
2	0	2	0	2	0	1	0	1	0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0
3	0	2	0	3	0	2	0	3	0	1	0	2	0	1	0	2	0	1	0	1	0	1	0	1
4	0	3	4	5	0	3	2	4	0	2	1	2	0	1	1	1	0	0	0	0	0	0	0	0
5	0	4	3	1	0	3	2	1	0	2	0	1	0	2	0	1	0	1	0	1	0	1	0	1
6	0	3	3	3	0	2	3	3	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0
7	1	0	7	6	1	0	3	3	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total dead	42	25	22	19	42	29	31	27	43	34	40	33	43	35	42	37	43	38	45	41	43	38	45	41
Total living	1	18	23	28	1	14	14	20	0	9	5	14	0	8	3	10	0	5	0	6	0	5	0	6
Standard deviation	0.35	1.58	2.48	1.69	0.35	1.28	1.41	1.60	0	1.12	1.06	1.49	0	1.13	0.74	1.67	0	1.12	0	1.38	0	1.12	0	1.38
X^2	19.52		0.66		13.65		1.29		10.05		4.89		8.82		4.04		5.34		6.14		5.34		6.14	
P	<0.01		0.5		<0.01		>0.2		<0.01		<0.05		<0.01		<0.05		0.02		>0.01		0.02		>0.01	

N = Normothermia.
NRx = Normothermia + penicillin.
H = Hypothermia.
HRx = Hypothermia + penicillin.
P values refer to difference between groups receiving penicillin.

TABLE IV.—SURVIVAL FOLLOWING EXPERIMENTAL PERITONITIS HYPOTHERMIA WITH 2 INJECTIONS OF PENICILLIN, ONE AT ONSET OF COOLING, THE OTHER 12 HOURS LATER

Experiment	*0 hours*				*12 hours*				*24 hours*				*36 hours*				*48 hours*				*60 hours*			
No.	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*
1	5	5	4	2	4	5	4	2	2	4	4	2	1	4	3	2	0	3	3	2	0	3	2	2
2	5	5	6	7	4	5	6	7	4	4	5	7	3	4	5	7	2	3	4	6	2	2	3	6
3	5	5	6	8	4	5	6	8	3	5	6	8	2	5	5	8	1	4	5	7	0	4	4	7
4	5	5	4	6	4	5	4	6	4	4	3	6	3	4	3	5	2	4	2	5	1	3	2	5
5	5	5	7	6	4	5	7	5	3	4	6	5	2	4	6	4	0	3	6	4	0	3	5	3
6	6	6	10	10	5	6	10	10	4	5	10	10	3	5	9	10	2	5	9	9	1	4	8	9
Total dead	0	0	0	0	6	0	0	1	11	5	3	1	17	5	6	3	24	9	8	6	27	12	13	7
Total living	31	31	37	39	25	31	37	38	20	26	34	38	14	26	31	36	7	22	29	33	4	19	24	32
Standard deviation	.40	.40	2.23	2.66	.40	.40	2.23	2.76	.81	.51	2.42	2.73	.81	.51	2.21	2.89	.98	.68	2.48	2.43	2.12	.75	2.26	2.58
X^2 N_{Rx} vs. H_{Rx}		0				0.80				4.05				1.21				1.84				3.76		
P						<.50				>.10				>.50				>.30				<.20		

Experiment	*72 hours*				*84 hours*				*96 hours*				*108 hours*				*120 hours*				*132 hours*			
No.	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*	*N*	*NRx*	*H*	*HRx*
1	0	2	2	2	0	2	1	1	0	1	0	1	0	1	0	1	0	1	0	0	0	1	0	0
2	1	2	3	6	1	1	2	6	1	1	2	6	1	0	0	6	1	0	0	6	1	0	0	6
3	0	4	0	7	0	2	0	5	0	0	0	2	0	0	0	1	0	0	0	1	0	0	0	0
4	0	3	1	4	0	2	1	4	0	2	0	4	0	2	0	2	0	2	0	1	0	2	0	1
5	0	2	5	3	0	2	4	2	0	1	2	1	0	1	1	1	0	1	0	0	0	1	0	0
6	0	4	7	9	0	1	4	8	0	0	0	6	0	0	0	3	0	0	0	2	0	0	0	1
Total dead	30	12	19	8	30	21	25	13	30	26	33	19	30	27	36	25	30	27	37	29	30	27	37	31
Total living	1	19	18	31	1	10	12	26	1	5	4	20	1	4	1	14	1	4	0	10	1	4	0	8
Standard deviation	.40	1.0	2.22	2.64	.40	.52	1.4	2.57	.40	.55	.88	2.32	.40	.67	.40	1.96	.40	.67	0	2.0	.40	.67	0	2.1
X^2 N_{Rx} vs. H_{Rx}		2.80				8.18				8.78				4.78				1.75				0.70		
P		<.30				<.02				<.02				<.10				<.50				.70		

P values refer to difference between groups receiving penicillin, the one normothermic (NRx) the other hypothermic (HRx).

chemotherapy alone (15 per cent survival). This difference is statistically insignificant ($p = .80$ at 132 hours).

DISCUSSION

The actual merits of hypothermia in the treatment of infection are extremely difficult to judge from the reported clinical studies. Most of these gravely ill patients have received concomitant drug therapy, have been variously narcotized, and have been subjected to various degrees of hypothermia.

Considering its extensive clinical trials, experimental evaluation of the effect of hypothermia on infection has been meager. The earlier studies on the effect of body chilling on infection are not comparable to generalized body hypothermia induced during anesthesia when there is minimal stress from the stimulus of cold. Balch found that generalized body hypothermia increased the length of survival of 26 rats from peritonitis produced by cecal contamination but that hypothermia plus dihydrostreptomycin offered no more protection than when streptomycin was used alone. Grechishkin, quoting a number of other Russian authors, showed that 46 hypothermic rabbits withstood staphylococcal septicemia better than 23 controls. Fedor and associates showed that hypothermic and normothermic dogs intravenously inoculated with Escherichia coli and Aerobacter aerogenes were able to rid the blood within 6 hours of 99 per cent of injected pathogens with equal facility. Sanders, Crawford, and DeBakey report quite the opposite effect and have shown that generalized hypothermia increases the pathogenicity of pneumococci injected intradermally in rabbits. It is not clear why their findings differ so markedly from those of others.

This study clearly shows the protective effect of hypothermia on both length and per cent of survival of animals given a peritoneal infection with pneumococci. There is, however, no significant benefit of combining hypothermia with a bactericidal antibiotic such as penicillin.

The mechanism of the protective effect of hypothermia remains obscure. It could result from increased host resistance or to diminished bacterial virulence. In vitro studies demonstrate a prolongation of the lag phase of bacterial growth which presumably also occurs in vitro during hypothermia. Should host immune reactions remain unaltered during hypothermia an over-all protective effect on the host would result as bacterial multiplication is delayed. Inasmuch as penicillin is effective only on the multiplying organism the ineffectiveness of combining hypothermia with penicillin could also be explained on this basis, since hypothermia delays the very phase of bacterial growth upon which penicillin is most effective.

SUMMARY

1. Hypothermia at 19 degrees C. for 24 hours increases the percentage of survivals of mice infected with pneumococcal peritonitis by 24 per cent compared to normothermic controls.

2. Under these experimental conditions the addition of hypothermia to penicillin therapy has no therapeutic value.

3. The possible mechanisms of the protective action of hypothermia have been discussed.

REFERENCES

1. Balch, H. H., Noyes, H. E., and Hughes E. W. The influence of hypothermia in experimental peritonitis. Surgery, 1955, 38: 1036.
2. Eiseman, B., Malette, W. G., Wotkyns, R. S., Summers, W. B., and Tong, J. L. Prolonged hypothermia in experimental pneumococcal peritonitis. J. Clin. Invest., 1956, 35: 940.
3. Fedor, E. J., Fisher, E. K., Lee, S. H., Weitzel, W. K., and Fisher, B. The effect of hypothermia upon induced bacteremia. Proc. Soc. Exp. Biol., N. Y., 1956, 93: 510.
4. Grechishkin, D. K. The influence of hypothermia on the clinical evolution of experimentally induced sepsis (Russian). Eksper. Khir. Moskva, 1956, 1: 33.
5. Sanders, F., Crawford, E. S., and DeBakey, M. E. The effects of hypothermia on infection; an experimental study. Surgical Forum; Clinical Congress 1957. Vol. VIII. Chicago: American College of Surgeons, 1958.

P values refer to difference between groups receiving penicillin, the one normothermic (NRx) the other hypothermic (HRx).

ISOTOPIC LOCALIZATION OF THE PLACENTA IN PLACENTA PREVIA

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ACCURATE LOCALIZATION of the placenta is of considerable clinical importance in the management of obstetric patients with third trimester bleeding. The search for a safe, practical, and reliable radiologic method has interested numerous obstetricians and radiologists over the past 30 years. Weinberg (4), in an excellent review article on placentography, discussed 8 different techniques which have been employed, which fact is evidence that there is no single universally accepted method.

Clinical information as derived from accurate placental localization would be of most value in that group of pregnant patients with antepartum bleeding between the twenty-eighth and thirty-sixth week of gestation. The conservative or "expectant" management of placenta previa during this period seems well established both in this country and abroad. It is in these weeks that clinical diagnosis by intracervical digital examination may be ill-advised because of the danger of increased bleeding which may precipitate definitive therapy before the fetus has reached a developmental stage of relatively safe viability. Ancillary diagnostic procedures are not meant to supplant vaginal examination in patients whose clinical state demands immediate therapy. Such methods would, however, be important in establishing a diagnosis as well as in avoiding unnecessary hospitalization and unwise manipulation in those patients in whom bleeding occurs during the early part of the third trimester.

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Most radiographic methods are stated to have relatively high degrees of accuracy (75 to 95 per cent) but all have specific limitations and disadvantages. Many include special techniques which are difficult to execute and produce films which require interpretation by an experienced radiologist. Furthermore, every method involves manipulation and movement which one would prefer to avoid in the bleeding patient. Perhaps the primary disadvantage of all radiographic methods is the matter of irradiation to the patient's ovaries and the fetus.

There is increasing and alarming evidence that apparently innocuous diagnostic irradiation to the pregnant patient may cause genetic damage to the fetus and may be associated with subsequent leukemia in the child. Howard in trying to determine a "safe" genetic dose of irradiation stated that "to regard any gonad dose as 'permissible' seems to be unreasonable unless one implies only that one is sure that the advantages resulting from it outweigh certain damage . . . ." Certainly a method of placental localization which would represent a simplification in technique and an improvement in accuracy and safety would be most desirable.

In 1951, Browne (1, 2) reported the first nonradiographic method of localizing the placenta by using radioactive sodium in a large number of cases. The author was mainly interested in localizing the placenta for research purposes, but suggested certain clinical applications of such a procedure and reported correct localization in 32 of 43 pregnancies complicated by placenta previa. Browne's findings were confirmed

in this country by Weinberg and associates (5, 6) who have recently reported their results in 52 cases. These authors suggested that radioiodinated (I^{131}) human serum albumin would further increase the accuracy and safety of isotopic localization.

In this article our results in the first 30 cases which were studied to test the accuracy and simplicity of this method are presented as well as certain modifications in technique and in interpretation.

METHODS AND MATERIALS

Five microcuries of radioiodinated human serum albumin are injected intravenously into the selected patient. After allowing 2 minutes for the isotope to mix in the circulating blood, radioactivity measurements are made over the abdominal surface of the gravid uterus. This surface is divided into simple anatomic areas for the purpose of counting, as depicted in Figure 1. Counts are also obtained over the xiphoid before and after scanning the uterus.

The procedure is based on the fact that the placenta represents a relative "pool" of maternal blood in the gravid uterus. If, therefore, a radioactive tracer is injected intravenously the activity recorded over the placental site should be increased if the isotope is confined to the maternal vascular compartment.

A standard scintillation counter with wide angle aperture is used to detect the gamma-radiation from the injected tracer. Successive counts are taken with the counting aperture placed flush with the skin over the center of each area.

This study was carried out on 30 patients admitted to the obstetric services of the University of California Hospital at Los Angeles and the Harbor General Hospital for elective repeat cesarean section and in patients who had third trimester bleeding. The only other factor of selectivity was the presence of one of us to carry out the diagnostic procedure. The actual placental site was determined in each case at subsequent cesarean section (25 cases) or vaginal delivery (5 cases) by direct visualization or by manual removal of the placenta. Of the 30 patients studied, 9 had third trimester bleeding. In 4 cases this bleeding was due to placenta previa and in 5 patients the bleeding was associated with premature separation of a normally implanted placenta.

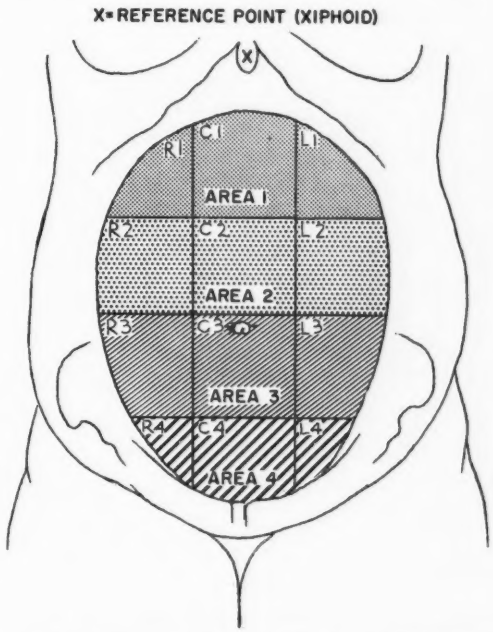

FIG. 1. Anatomic sketch of the gravid uterus illustrating the areas which are counted.

RESULTS

Because of the wide variation in observed counts for individual patients, the number of counts over the xiphoid was used as a reference point, and was arbitrarily chosen to represent 100 per cent. The values in terms of counts per minute in each section were then expressed as a percentage of the counts observed over the xiphoid. The means and standard deviation for the percentages obtained in areas 1, 2, 3, and 4 (Fig. 1) in the absence of the placenta were compared with the identical data from cases in which the placenta was present in these areas (Table I). The accuracy of predicting the location of the placenta was greatest in

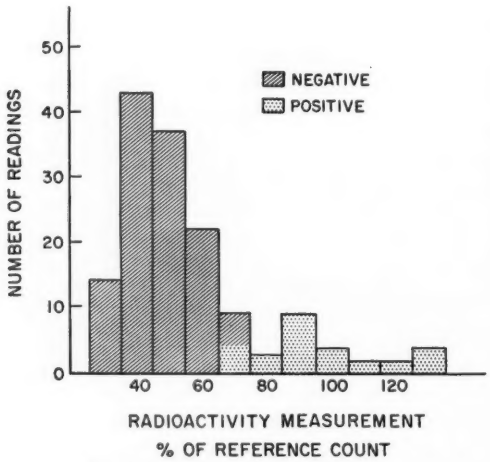

FIG. 2. The distribution of radioactivity measurements (153 readings) in areas 3 and 4. Negative readings refer to those in which the placenta was not present in the area. Positive readings are those in which the placenta was found to be in the specified area.

areas 3 and 4 where the difference between negative and positive values was highly significant. Fortunately the greatest degree of discrimination occurred in the anatomic area of greatest clinical importance, i.e., the lower uterine segment. The distribution of 153 readings over areas 3 and 4 is shown graphically in Figure 2. In the patients studied, there was no difficulty in determining the position of the placenta in each case

TABLE I.—COMPARISON OF RADIOACTIVITY MEASUREMENTS IN THE PRESENCE AND ABSENCE OF THE PLACENTA

Area	*N*	*M*	*s*	*t*
1 (R1 C1 L1)				
Placenta present	10	113.6	66.9	2.04
Placenta not present	26	70.1	15.1	
2 (R2 C2 L2)				
Placenta present	18	97.9	22.1	6.20
Placenta not present	47	62.2	17.1	
3 (R3 C3 L3)				
Placenta present	19	96.5	18.4	9.11
Placenta not present	48	54.6	12.6	
4 (R4 C4 L4)				
Placenta present	8	100.5	14.8	9.40
Placenta not present	78	50.1	10.1	

N, Number of readings.
M, Means values expressed as per cent of reference counts.
s, Standard deviation.
t, t-Test for difference in means.

when one compared the relative activity in each section. An attempt has been made to select an arbitrary cutoff point which would be applicable in all cases and which would necessitate counting only areas 3 and 4. Distribution-free tolerance intervals were computed from the observations shown graphically in Figure 2. One may state with great confidence that, in 90 per cent of all patients with a normally implanted placenta, readings in areas 3 and 4 will range between 35 and 69 per cent and that 90 per cent of patients with placentas in this area will give readings in the range of 73 to 130 per cent. The precision is not as sharp over the fundus of the uterus which is probably due to the increase in scatter radiation from the liver, spleen, and heart.

Two actual radioactivity patterns on patients with third trimester bleeding are reproduced in Figures 3 and 4.

DISCUSSION

Although the ultimate evaluation of the reliability of this technique rests upon more extensive clinical trials, it would seem that certain preliminary remarks are warranted.

For this method of placental localization to be of practical value, one must demonstrate that it is simple, safe, and reliable and that it obviates some of the limitations and disadvantages of other techniques of placentography.

In regard to the matter of safety, the chief considerations would seem to be the amount of irradiation to fetal tissues and the maternal ovaries. The amount of irradiation associated with roentgen placentography is extremely variable and frequently expressed as a skin dose. This may be as much as 10 to 15 roentgens with some techniques. Weinberg (6) estimated the radiation dose to the fetus as being approximately 1.0 roentgen from a soft tissue radiograph and calculated that the fetal dose would be reduced to one-fiftieth of this amount by using 5.0 microcuries of radioactive iodinated human serum albumin.

If one were to assume that 5.0 microcuries

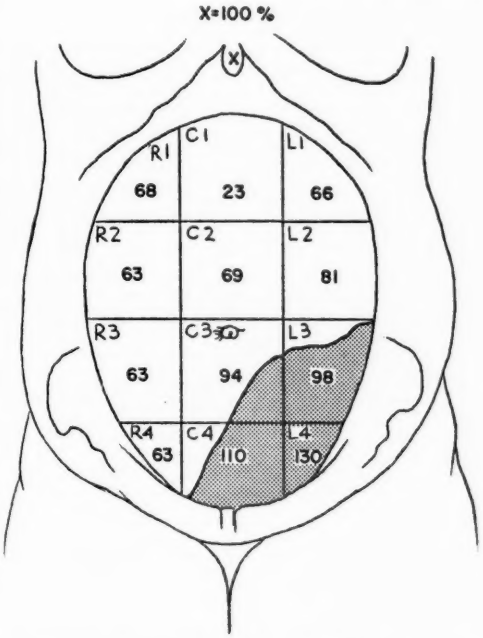

FIG. 3. Placental localization in patient J. P. on February 8, 1957; expected date of confinement April 7. Clinical diagnosis—third trimester bleeding. Five microcuries of radioactive iodinated human serum albumin used. Interpretation—placenta previa, *C3 L3-C4 L4.* Clinical findings as depicted.

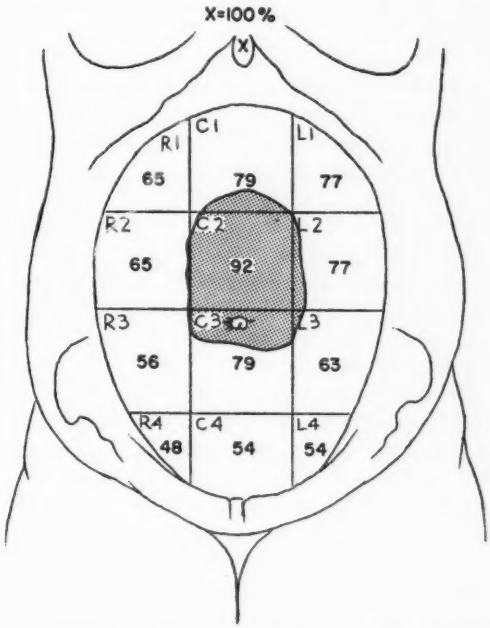

FIG. 4. Placental localization in patient B. G. on June 11, 1957; expected date of confinement July 4. Clinical diagnosis—third trimester bleeding. Five microcuries of radioactive iodinated human serum albumin used. Interpretation, not placenta previa, *C2 C3.* Clinical findings, as depicted—premature separation.

of iodinated human serum albumin were diluted in a blood volume of 3,000 milliliters and that the fetus occupied a position in the center of a sphere which was constantly being bathed by one-half of the maternal blood volume, we calculate that the maximum fetal dose to total decay would be approximately 70 milliroentgens. If the pregnancy were terminated within 24 hours, as many of them are, the dose would be less than 0.35 milliroentgen. These would appear to be maximum estimates and, therefore, the amount of radiation delivered to the fetus in this technique is significantly less than with the conventional methods.

An advantage of considerable practical importance is the fact that the bleeding patient does not have to be moved from her bed during this procedure. Counting can even be done in the labor room, but we have elected to transport the patient in her bed to the isotope laboratory rather than to move the equipment.

The isotopic substance and counting equipment are readily available in most hospitals with facilities for doing diagnostic isotope studies. Iodinated human serum albumin is available commercially, is relatively inexpensive, and has a half-life of 8.0 days so that it is feasible to have it in stock at all times. No radioactivity has been demonstrated in the infants with this dose, and it is probable that placental transmission is very slow because of the high molecular weight of the tracer substance.

It requires 10 to 15 minutes to scan the uterus and the results are immediately available. There are no films to be developed and consultation with a radiologist

for interpretation of results is therefore unnecessary.

The accuracy of radiologic determination of the placental site by placentography is stated to vary between 75 and 95 per cent yet some departments rarely use placentography as a diagnostic aid because of the disadvantages previously mentioned. Weinberg (6) reporting on 52 cases using radioactive sodium and iodinated human serum albumin stated that the placenta was localized correctly in all proved cases. In 3 instances, the results were classified as equivocal.

In this series, the position of the placenta was correctly localized in all cases in which it was later found in areas 3 and 4. When the placenta was located on the posterior surface of the fundus in the midline, counts in all areas were at the base line level, and localization was by exclusion. Most posteriorly implanted placentas were detectable by an increase in activity over one or the other lateral margin of the uterus. It is conceivable that a low-lying placenta in the midline posteriorly could be missed; however, in the only such case encountered in this series, a posterior placenta previa, gave a positive reading in all 3 subsections of area 4.

Further investigation has been undertaken with a reduction in the amount of isotope and improvement in instrumentation in an attempt to increase the precision of localization in the fundus.

SUMMARY AND CONCLUSION

1. A suggested isotope technique for the localization of the placenta has been evaluated and substantiated as a practical diagnostic method for detecting placenta previa.

2. Radioactivity surveys over the abdominal surface of the gravid uterus were employed by using 5.0 microcuries of radioactive iodinated human serum albumin and a scintillating counter as the detector of the gamma radiation.

3. Thirty patients were studied in this manner and the findings were correlated with the anatomic position of the placenta by manual exploration of the uterus at delivery.

4. An over-all diagnostic accuracy of 100 per cent was obtained in areas 3 and 4 for the cases in this study.

5. The test is comparatively simple, safe, rapid, and reliable.

REFERENCES

1. Browne, J. D. McC. Localization of the placenta by means of a radioactive isotope. Postgrad. M. J., Lond., 1952, 28: 442.
2. Idem. Localization of the placenta by means of radioactive sodium. Proc. R. Soc. M., Lond., 1951, 44: 715.
3. Howard, A. An attempt to assess the genetic changes resulting from the irradiation of human populations. Brit. J. Radiol., 1956, 29: 270.
4. Weinberg, A. Placentography; the radiological determination of the placental site. Obst. Gyn. Survey, 1955, 10: 461.
5. Weinberg, A., Rizzi, J., McManus, R., and Rivera, J. Localization of the placental site by a radioactive sodium isotope (Na_{24}); preliminary report. Obst. Gyn., 1956, 8: 396.
6. Idem. Localization of the placental site by radioactive isotopes. Obst. Gyn., 1957, 9: 692.

EDITORIAL

POSTOPERATIVE COMPLICATIONS

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POSTOPERATIVE COMPLICATIONS of one type or another account for the majority of postoperative deaths. Obviously, it is the surgeon's aim to reduce these complications to an absolute minimum. In past years, certain postoperative complications, such as pulmonary embolism, were considered to be unavoidable; others were thought to be more or less inevitable in a certain percentage of patients. Such thoughts were held because the true factors responsible for these complications were not well appreciated. Under such circumstances, postoperative mortality rates were high by current standards for most surgical procedures. Furthermore, surgeons were less alert to the importance of early and accurate recognition of postoperative complications before they became full blown. At the same time, treatment was not always well founded on a scientific basis. Fortunately for the patient, improvements have been made in all of these factors, but plenty of opportunity still exists, of course, for further improvement. Advances were first made in diagnosis and subsequently in knowledge of etiology and treatment. It actually is the more definite knowledge of the etiologic factors involved in postoperative complications that has led to more effective treatment and, of even more significance, the prevention of complications.

Postoperative complications may be divided into two main categories, namely local, which includes those related to the operation and the disease for which the operation was performed, and systemic, which may be entirely unrelated to the primary surgical problem. The former group occurs in relationship with the particular lesion being treated and the technical aspects of the operation concerned, whereas the latter may be related to disease elsewhere in the body, such as cardiac, pulmonary, or renal abnormalities, or to a more generalized condition, such as imbalance of electrolytes, decreased blood volume, or hypoproteinemia. It is obvious that both types of complications may be active in the same patient. As for the local factors that cause trouble during the postoperative period, it appears certain that every surgeon strives to execute each surgical procedure with the utmost care and technical ability. Adequate training and experience are obvious prerequisites for such accomplishments. Likewise, advances in anesthesiology have been most helpful in reducing complications both during and after operation.

No doubt exists that operative morbidity and mortality rates can be reduced further by greater attention to prevention, recognition, and adequate treatment of systemic abnormalities. A "check list" that is always kept in mind may prevent the surgeon from overlooking what should be an important part of preoperative preparation or prophylactic postoperative care. Such a list should include certain broad categories, such as significant traits in the patient's family, complications the patient has experienced after a previous operation, and the status of the important systems in the body, such as the

cardiovascular, pulmonary, and renal systems. In addition, the list should include considerations such as recent loss of weight, presence of infection, nutritive status, especially with regard to stores of protein, hydration, balance of electrolytes, anemia, blood volume, previous administration of cortisone, and drug allergies. If thought is given to such items prior to operation, the desirability of certain corrective or prophylactic preoperative measures will become apparent for almost every patient who has serious disease.

Thus, a number of factors, such as a history of previous phlebitis, varicosities in the lower extremities, prolonged rest in bed, infection, obesity, neoplasm, anemia, and certain types of operation, may predispose in varying degrees to postoperative thromboembolic complications. When one or perhaps several of these factors are known to exist in a given patient, careful attention should be given to postoperative prophylactic measures directed toward prevention of thromboembolic disease. A patient who is suspected of having deficiency in the coronary circulation should be protected against periods of hypotension, inadequate oxygenation, hypervolemia, and other undesirable states. Postoperative administration of an isotonic solution of sodium chloride should be curtailed in any patient who has had cardiac failure, pulmonary edema, nephrosis, or other similar states. A patient who has a productive cough should receive adequate preoperative treatment to reduce cough and bronchial secretions; particular attention should be directed to closure of the incision, and perhaps bronchoscopy should be done at the conclusion of the operation. A postoperative regimen to prevent atelectasis is also indicated. Of great importance is attainment of an adequate preoperative nutritive status so that if the patient is starved for a few days after operation, as is usually the case to a greater or lesser degree, he will not be subjected to levels of nutrition that are so low as to be inconsistent with satisfactory healing.

With increasingly widespread use of cortisone, one must remember that administration of certain amounts of this agent will result in adrenal atrophy of variable duration, so that the function of these glands is inadequate for the extra stress produced by an operation. Proper preoperative preparation with cortisone may be indicated in some of these patients. One should keep in mind the possible undesirable sequelae of certain aspects of treatment that we surgeons may recommend, such as rest in bed, intravenous administration of fluids, use of indwelling tubes and catheters, enemas, prolonged and repeated use of sedatives, excessive numbers of laboratory tests, use of medicaments that produce nausea and thereby interfere with adequate nutrition, and many similar considerations.

Obviously, many other factors exist that may contribute to the likelihood of postoperative complications that vary in significance from patient to patient. The important point is to think of these factors and make every possible effort to correct them prior to operation. At the present time, our greatest effort should be directed toward prevention of postoperative complications. Recognition and treatment then become necessary in a decreasing number of patients and only when our efforts for prevention fail.

THE SURGEON AT WORK

EXTRAPERITONEAL CESAREAN SECTION

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THIS ARTICLE was written primarily to portray the essential steps of an extraperitoneal cesarean section as developed at the Woman's Hospital Division of St. Luke's Hospital in the last 125 consecutive extraperitoneal cesarean operations.

Fritz Frank of Cologne began his efforts to circumvent intraperitoneal invasion in 1906. Frank did not definitely state that he actually performed an extraperitoneal operation, but he called attention to the old Physick principle of 1824 as a possible approach to the lower segment. It was Hugo Sellheim who in 1908 first performed a true extraperitoneal cesarean section according to the Physick principle, separating the anterior peritoneal fold from the dome of the bladder and exposing the entire lower segment by displacing the bladder downward. He succeeded in his first 3 cases, but he soon became aware of the surgical difficulties due in part to his lack of an exact knowledge of the fascial planes. Furthermore, he was not aware of the fact that the relationship between the bladder and the peritoneum was not identical in all cases.

In the same year Latzko, impressed with the difficulties encountered in separating the bladder dome from the anterior peritoneal fold and virtually admitting the procedure was impossible, devised his own method of extraperitoneal cesarean section. His operation differed in that his approach was a lateral paravesical fold displaced toward the midline and held in place by a retractor. The procedure exposed the left half of the lower segment which was incised longitudinally to permit delivery.

In 1940 the Physick-Sellheim operation was revived in America. Working independently, Ricci of New York and Waters of Jersey City, evolved methods which have simplified the separation of the bladder dome from the peritoneal fold. Both investigators have stressed the necessity of a clear understanding of the relationship of the fascial planes to the lower segment, anterior or posterior bladder surfaces (capsule), and the peritoneal fold.

Both authors preferred the Munro-Kerr incision, knowing from experience that the Latzko operation with its longitudinal incision, on occasion extending downward into a vascular network of vessels or extending upward, tears into the peritoneal cavity and thus defeats the object of a true extraperitoneal cesarean section.

The extraperitoneal cesarean section has never been popular among the large group of obstetricians. Their main objections appear to be the technical difficulties encountered; that injuries to the bladder and ureter are too frequent, that it is time-consuming, and finally that the increasing use and demonstrated effectiveness of antibiotics have rendered it obsolete or unnecessary.

We believe that we have succeeded in minimizing the objections by an extraperitoneal approach to the lower uterine segment which reduces the incidence of injuries to the bladder or peritoneum. A technique is described which has reduced the time element to a total of 40 to 45 minutes, even when performed by relative beginners such as resident house officers, thus

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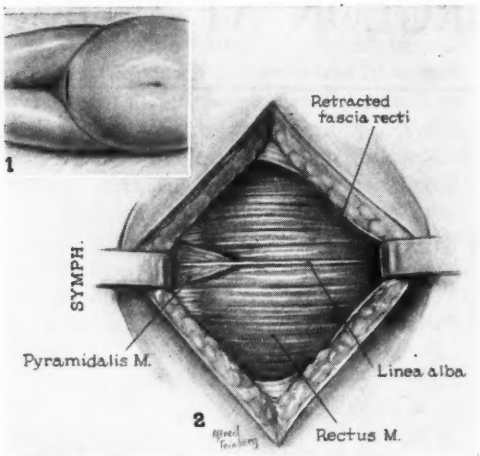

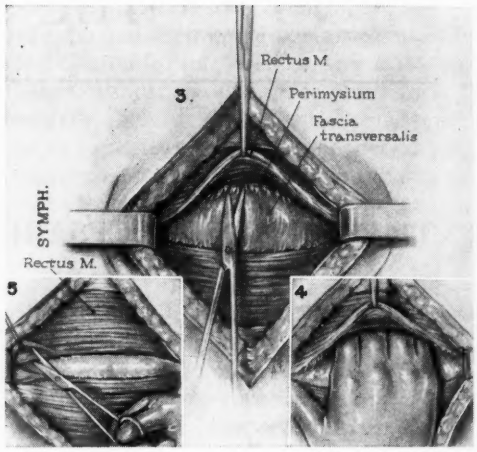

FIG. 1. The Pfannenstiel incision employed in this procedure.

FIG. 2. The subcutaneous tissues and fascia have been split transversely to expose the bellies of the underlying rectus abdominis muscles.

FIG. 3. The rectus muscles have been incised longitudinally and are being separated from the underlying transversalis fascia.

FIG. 4. The dissecting hand completes the separation of the muscles from the fascia.

FIG. 5. The rectus is partially detached from its attachment to the symphysis to afford more room.

competing in time elapsed with the low flap operation.

SURGICAL TECHNIQUE

A Pfannenstiel incision is made, and the upper bladder surface and dome are exposed as illustrated in Figures 1 to 5.

Liberation of the anterior peritoneal fold from the upper bladder surface and dome. The semiempty bladder should be visualized and felt. It lies underneath the widespread fascia transversalis and is completely enveloped (anteriorly and posteriorly) by the vesical fascia. Finger massage of the bladder with its fascial coats helps to contract this viscus and thus to prevent bladder injuries. With 2 Halsted clamps, the fascia transversalis and the sublying anterior vesical fascia are grasped a good inch below the bladder dome, exactly at the midpoint. Between these 2 clamps, all the laminated layers of the fasciae are incised except the layer closest to the musculature of the bladder so that a protective terminal lamination is left on the bladder to minimize injury to the tortuous superficial vesical vessels. The incision is enlarged into either paravesical areas in an arc-like manner, curving downward behind Poupart's ligament.

Three Halsted clamps are placed on the upper decapsulated margins of the bladder and the bladder dome is gently teased from its attachments to the fascia vesica (capsule). This blunt separation is extended well over the bladder dome so as gradually to arrive at the left paravesical space. Thus is completed the first major step of the operation—the liberation of the anterior peritoneal fold with its fascial coverings from the anterior surface of the bladder and bladder dome.

Liberation of the posterior peritoneal fold from the posterior surface of the bladder and lower uterine segment. The left paravesical fossa is exposed with the aid of a Bissel retractor. The padding fatty tissue is frayed upward with a sponge stick while the bladder is gently retracted downward and laterally. The posterior peritoneal fold then appears as a grayish-white transparent apron resembling a flattened empty hernial sac. A good inch below the fold, the transparent fascia uteri is picked up and incised sufficiently to permit the insertion of index and middle finger. The fingers are swept from left to right. The bladder is separated and elevated from its lower segment bed. This maneuver reveals that the bladder is freed laterally and up to one-half the circumference of the dome. A second small retractor pulls the bladder to the right, thus exposing the lower uterine segment. Thus is completed the second major step of the opera-

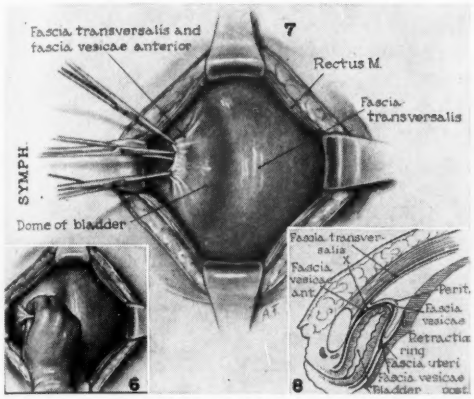

FIG. 6. The semiempty bladder is visualized and felt.

FIG. 7. The fascia transversalis and anterior vesical fascia are grasped a good inch below the bladder dome, at the midpoint.

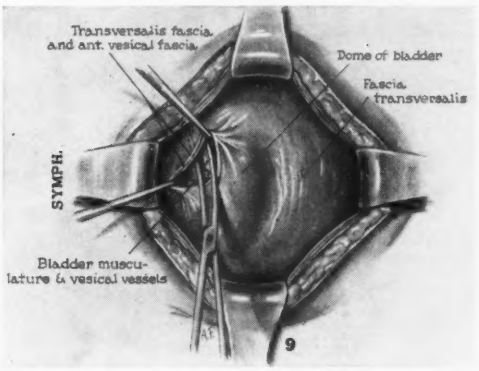

FIG. 8. A sagittal view of the relationships of the fasciae to the peritoneal folds.

FIG. 9. The fascia transversalis and anterior vesical fascia are incised down to the layer of bladder musculature.

tion—the liberation and upward displacement of the posterior peritoneal fold and downward and lateral displacement of the bladder.

The midpoint of the lower segment is located and a 1 inch transverse incision is made. The membranes are ruptured and the amniotic fluid is siphoned off. The incision is lengthened on both sides of the midpoint for 3 inches. At the extreme ends of the incision, sutures are inserted to act as guides in the repair and for hemostasis.

When the lower segment incision is completed, all retractors are removed. The occiput is located and the vertex is rotated to an occipitoanterior position by applying Haig-Ferguson forceps accurately. The vertex is delivered by abruptly extending the latter, using the right hand as a vectis. It should be emphasized that manual pressure on the fundus from above is contraindicated, lest the posterior peritoneal fold be torn.

MATERIALS AND METHODS

During the period 1946 to 1956 a total of 3,381 cesarean sections were done at the Woman's Hospital Division of St. Luke's Hospital. Extraperitoneal cesarean section was performed in 136 cases, or 4 per cent of all abdominal deliveries; of these, 125 were done according to the technique developed at the Woman's Hospital Division of St. Luke's Hostal. Both the private and the ward services are represented. The ages of the patients ranged from 16 to 45 years. There were 96 primiparas and 29 multiparas in the group. In 48 cases the operation was performed by an attending physician; in 77, by a resident. The average operating time was 45 minutes.

RESULTS

The indications for abdominal delivery are detailed as follows: Cephalopelvic disproportion with trial of labor was the determining factor in 64 cases. Breech with trial of labor was the indication in 8 cases, brow with trial of labor in 2 cases, and fetal distress, inertia, transverse lie, rheumatic heart disease, failed forceps, and twins accounted for 1 each. There were 45 elective extraperitoneal operations, of which 17 were for previous cesarean sections, 13 were elderly primipara, 5 were for cephalopelvic disproportion proved by x-ray pelvimetry prior to labor, 4 for unfavorable breech as demonstrated by x-ray studies, 2 for previous penetrating myomectomy, and 1 each for placenta previa, previous bulbar poliomyelitis, premature rupture of the membranes and amnionitis, and poor obstetric history (2 previous stillbirths).

In the group of 64 who had cephalopelvic disproportion with trial of labor, there were 57 with ruptured membranes prior to delivery. In this group of 57 the average length of time of ruptured membranes was 20 hours, and the range was from 1 to 77 hours. Of these, there were 22 patients with membranes ruptured longer than 24 hours, and there were 7 patients

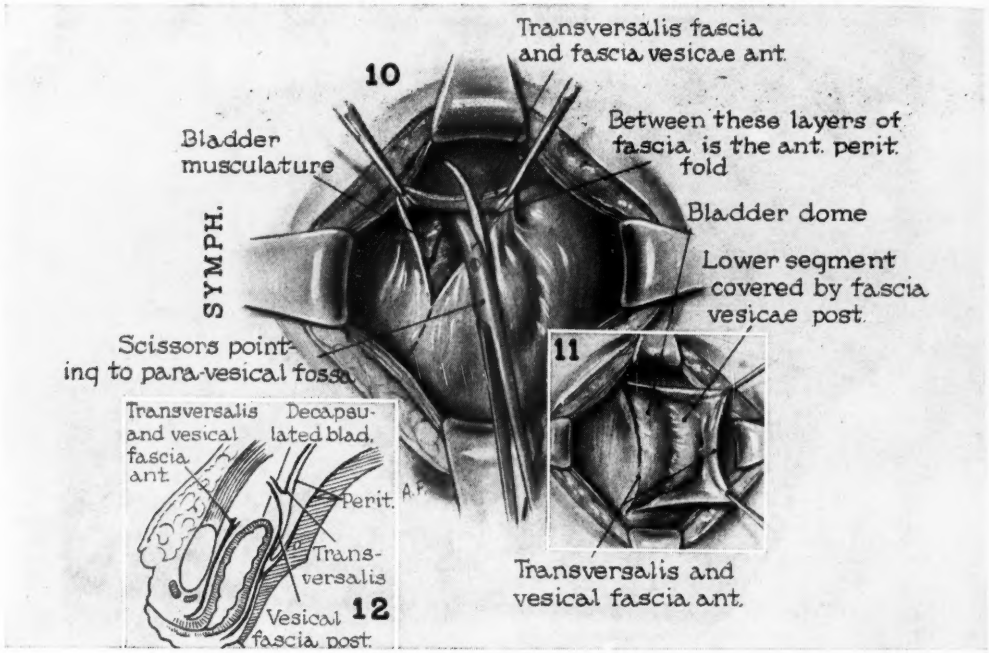

FIG. 10. The incision is carried to the paravesical fossa on each side.
FIG. 11. The transversalis fascia and the anterior vesical fascia containing the anterior peritoneal fold have been reflected from the bladder.
FIG. 12. A sagittal view of the procedure described in Figure 11.

with frank infection prior to delivery despite the administration in 4 cases of antibiotics in labor; these 7 cases are of especial interest and are described later in more detail.

Morbidity as defined by the Committee on Maternal Welfare was limited to 19 cases, or 15 per cent. Of these, 7 were due to major wound infections, 2 to aspiration pneumonias, 1 to pyelonephritis, and 1 to intestinal obstruction complicated by bilateral parotitis; there were 8 genital tract infections. In addition, there were 12 minor wound infections without morbidity and all occurring in the drain site. Complications in the series numbered 21 cases, 16.8 per cent. There was 1 instance of serum hepatitis which developed 3 months after operation (in this case a transfusion with 500 c.c. of whole blood had been given on the day prior to surgery because of anemia) and 1 of postoperative cardiac decompensation in an old rheumatic heart disease. There was only 1 case of postoperative distention which in fact was due to a mechanical obstruction of the small bowel caused by adhesions and necessitating laparotomy after intestinal decompression by Miller-Abbott tube had failed. There were 9 cases in which the peritoneum was opened (7.2 per cent), and in all cases this was quickly recognized and easily sutured. The bladder was opened inadvertently in 7 cases (5.7 per cent), and in all cases this was easily repaired and catheter drainage was instituted postoperatively with no complications resulting from this accident. There were 3 instances of postpartum hemorrhage—1 in the presence of uterine atony which responded to oxytocics, 1 uterine atony which did not respond to oxytocics necessitating supravaginal hysterectomy at the time of section, and 1 case was due to a bleeding vessel in an angle of the uterine incision which had to be religated several hours postoperatively. There were no instances of extension of the Munro-Kerr incision and no instances of exposure of or damage to the ureter.

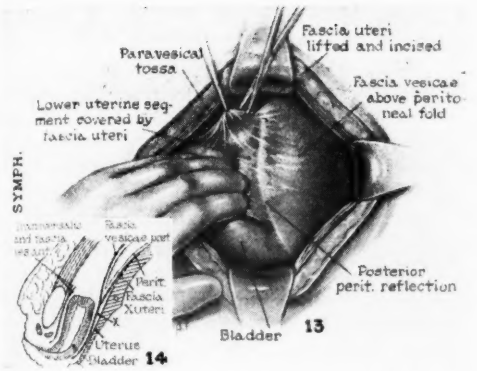

FIG. 13. The posterior peritoneal fold has been identified and the fascia uteri is incised to permit bladder to be swept off its lower segment bed. With release of this fascia the posterior peritoneal fold is displaced superiorly.

FIG. 14. A sagittal view of the operative procedure which is described in Figure 13.

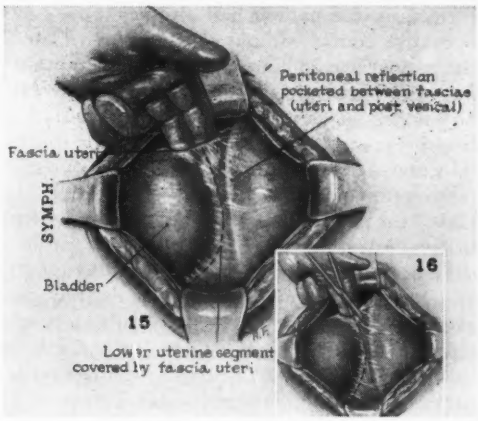

FIG. 15. The fascia uteri is incised.

FIG. 16. Another view of the incision of the fascia uteri.

In this series there was 1 maternal mortality which was classed as an anesthesia death since the patient was administered a rather larger dose of spinal anesthetic than is customarily given and was in complete respiratory paralysis and shock prior to the operation. She died soon after the skin incision, so that in effect a postmortem section was done to save the child. Nevertheless, the baby was a stillbirth. The perinatal mortality was 7, or 5.6 per cent of which 2 were premature births and 1 was the stillbirth described; of the remaining 4, 1 died of atelectasis, 1 of hyaline membrane disease, 1 of prolapsed cord, and 1 of undetermined causes.

Of special interest is the group of 7 patients with frank infection prior to delivery; in all cases the site of infection was assumed to be intrauterine in the absence of other positive findings. The patient in Case 1 had ruptured membranes for 36 hours and a temperature of 101 degrees F. prior to surgery; a healthy infant was delivered and aside from a right lower lobe

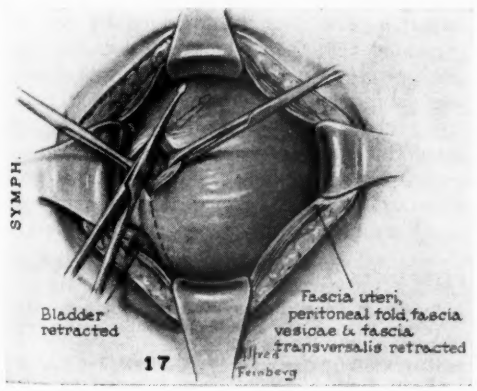

FIG. 17. The lower uterine segment is opened through a Munro-Kerr incision. The stay sutures placed at each angle of the incision are not pictured.

FIG. 18. The occiput has been manually rotated anteriorly and the Haig-Ferguson forceps have been applied in a cephalic application.

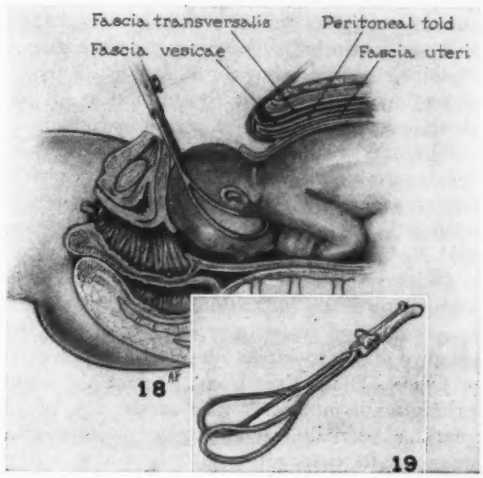

FIG. 19. The Haig-Ferguson forceps, a Simpson type, is the instrument of choice in this procedure.

atelectasis, the patient had an uneventful postoperative course without morbidity. In Case 2 the patient had 28 hours of ruptured membranes and a temperature of 102.4 degrees F. despite antibiotics in labor; she was delivered of a healthy infant, and aside from a minor wound infection at the drain site had an uneventful postoperative course without morbidity. In Case 3 the patient had 7 hours of ruptured membranes and an intrapartum temperature of 100.6 degrees F. She was delivered of a healthy infant, and her postoperative course was entirely uneventful. The patient in Case 4 has been previously discussed; she constituted the 1 death in this series. She had 30 hours of ruptured membranes and a temperature of 101.8 degrees F. before surgery; as described before, she was considered an anesthetic death, and the infant was stillborn. The patient in Case 5 had had ruptured membranes for an unknown length of time, and an intrapartum temperature of 104 degrees F. despite antibiotics administered in labor; she was delivered of a healthy infant and had a perfectly uneventful postoperative course without morbidity. The patient in Case 6 had 38 hours of ruptured membranes and a temperature of 102.4 degrees F. despite intrapartum antibiotics; the infant was a 9 pound 9 ounce male who died in 24 hours of atelectasis. The patient had a perfectly normal postoperative course without morbidity. The patient in Case 7 had ruptured membranes for 36 hours and a temperature of 101 degrees F. despite antibiotic therapy; she was delivered of a healthy infant, but had a morbid postoperative course due to endometritis and pelvic thrombophlebitis which were slow in responding to antibiotics. All patients were given antibiotics postoperatively.

The average hospital stay in this series was 9.3 days, is identical with that of the low cervical section series. In all but 3 patients drainage was with a Penrose drain in the paravesical fossa, and 2 of these 3 were morbid postoperatively.

Of interest is 1 case in this group which clearly demonstrates an indication for the extraperitoneal route of cesarean section aside from the classical one of intrapartum infection (potential or frank). The patient was a 21 year old white primigravida nullipara who at the age of 12 years had been subjected to a total colectomy and ileostomy for congenital multiple polyposis. She had a normal antepartum course, and had 13 hours of good labor with unsatisfactory progress. The attending obstetrician believed cesarean section was indicated, and elected the extraperitoneal route in order to avoid encountering the inevitable postoperative intra-abdominal adhesions, as well as to avoid disturbing the perfectly functioning ileostomy. A 6 pound 15 ounce infant was delivered by the extraperitoneal route without difficulty, and the postoperative course was entirely uneventful.

SUMMARY

1. A technique of extraperitoneal cesarean section, developed at Woman's Hospital Division of St. Luke's Hospital, is described. The simplicity and ease of execution of this technique is based upon a thorough working knowledge of the relationships of the fasciae and peritoneal reflections overlying the lower uterine segment at or near term.

2. One hundred and twenty-five consecutive extraperitoneal cesarean sections executed by the method herein described are analyzed. Particular emphasis is placed upon the fate of patients with frank intrapartum infection. Morbidity and complications are reviewed, and the 1 mortality in this series is discussed.

CONCLUSIONS

We believe that the extraperitoneal cesarean section as executed by this simple rapid technique retains an important niche in the obstetric armamentarium. Its role need not be confined to the patient with potential or frank infection. This fact is illustrated by the case presented herein, in which it was thought advisable to remain outside of the peritoneal cavity when abdominal delivery was indicated. Finally, and perhaps most important, resident training should include instruction in the extraperitoneal technique, since many residents settle in small communities where the neglected obstetric case is still an infrequent but important problem.

REFERENCES

1. Frank, F. Die suprasymphysare Entbindung und ihr Verhaltniss zu den anderen Operationen bei engen Becken. Zbl. Gyn., 1907, 81: 46.
2. Latzko, W. Wien. klin. Wschr., 1908, 21: 737, 1033.
3. Ricci, J. V. Simplification of Physick-Frank, Sellheim principle of extraperitoneal cesarean section. Am. J. Surg., 1940, 47: 33.
4. Sellheim, H. Der Einfluss von Asepsis und Infektion auf die Technik der Entbindung durch Schnitt. Münch. med. Wschr., 1908, 55: 2207.
5. Waters, E. G. Supravesical extraperitoneal cesarean section. Am. J. Obst. Gyn., 1940, 39: 423.

SURGICAL ANATOMY IN LACERATIONS OF THE WRIST AND HAND

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INJURIES TO THE UPPER EXTREMITY have been shown to occur in increasing frequency in non-industrial areas. The popularity of power tools and the decentralization of industry cause trauma to a part of the body that must be treated by physicians unaccustomed to this type of injury.

An attempt has been made in this article to simplify the anatomy of the upper extremity, particularly as it appears in the living patient. A survey of injury to the wrist and hand, treated in a community hospital, is presented.

Textbooks of anatomy necessarily are technical and detailed in their description of structures of the hand and wrist. It is often difficult to translate such information from the textbook to the living patient. One must have ready knowledge of these structures to determine the extent of injury at the time that the patient is first seen in the emergency room.

The tendons on the dorsum of the hand can be easily seen under the skin. An injury to these structures must be suspected with any laceration of the skin overlying these tendons. This is especially true in lacerations over the knuckles. Because of the triangular expansion of these tendons over the knuckles, function at this joint is rarely lost even with extensive division of these tendons. Careful inspection of the wound will reveal an opened joint and hence a lacerated extensor tendon. Unless this injury over the proximal interphalangeal joint is recognized and treated, the split fibers of the extensor tendon slip around the side of the joint, and the knuckle herniates through the tendon resulting in a deformity. The radial nerve is not involved in injuries at the wrist because this nerve supplies only the long extensor muscles at their origin on the lateral epicondyle of the humerus. Because all muscles are innervated at their origin, nerve injuries must occur proximal to the origin of a muscle to cause its paralysis.

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Median nerve injury at the wrist is noted when the opponens pollicis muscle is paralyzed. The origin of this muscle is distal to the nerve injury and has isolated median innervation. The test for this muscle is the ability to touch the tip of the thumb to the tip of the fifth finger. Sensory disturbance is noted by impaired sensation of the pulp of the index finger, the area of isolated sensory distribution.

Motor function of the ulnar nerve is tested by the function of the interosseous muscles. These seven small muscles abduct and adduct the fingers. Isolated sensory distribution of the ulnar nerve is on the pulp of the fifth digit.

The patient's ability to flex the distal interphalangeal joint demonstrates an intact deep flexor tendon or the long flexor of the thumb. Arterial bleeding from a laceration at the side of the finger indicates digital nerve injury.

These well known tests for injuries at the wrist may be unreliable in the hysterical patient or the frightened child. One cannot rely completely on function tests to demonstrate tendon injuries. Even with a co-operative patient seven flexor tendons at the wrist may be divided and yet the patient have what might be considered normal function.

Unless one has frequent occasion to review the anatomy of the wrist, these structures are quickly forgotten. Before one can diagnose the distorted structures of an injured wrist, one must be able to recognize the appearance of a normal wrist. The best review of this anatomy can be made on one's own wrist.

With the wrist flexed against resistance, three tendons are readily seen on the flexor surface (Fig. 1). Because these three tendons are so superficial, they are commonly injured and can be used as keys to structures immediately deep to them.

These three tendons are:

1. The tendon of the palmaris longus muscle occupies the central position at the wrist and continues on into the palmar fascia. This struc-

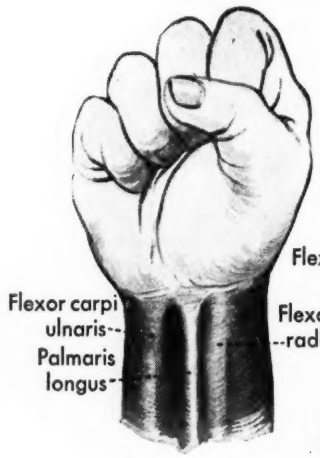

FIG. 1.

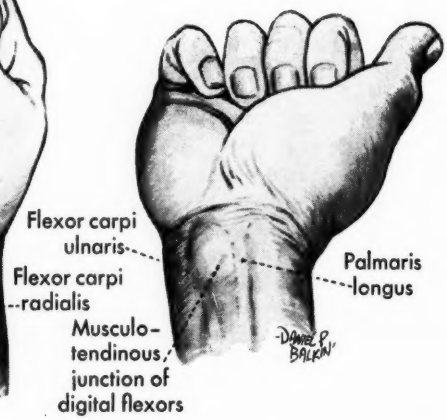

FIG. 2.

ture is present, however, in only 80 per cent of wrists. Therefore, it has no important function. Our major concern with an injury of this type is the median nerve which lies immediately deep to the palmaris longus tendon. The median nerve is the most important structure in the wrist and is frequently injured when the palmaris longus tendon is divided.

2. The tendon of the flexor carpi radialis muscle is a stout tendon lying immediately radialward to the palmaris longus tendon and inserts into the base of the second metacarpal bone. Deep to this structure is the tendon of the long flexor of the thumb. The tendon of the long flexor of the thumb and the median nerve, therefore, lie side by side. With division of the flexor pollicis longus, the thumb loses its grasping function and becomes useless.

3. The tendon of the flexor carpi ulnaris muscle occupies the extreme ulnar side of the flexor surface of the wrist and inserts into the pisiform bone. With the wrist passively flexed, this structure is easily seen and can actually be pinched between the thumb and index finger. Deep to this tendon are the ulnar nerve and artery. When this tendon is severed one should actually demonstrate an intact ulnar nerve because this nerve is so closely associated. Hemorrhage from the ulnar artery further demonstrates the proximity of the injury to the ulnar nerve.

It will be noted (Fig. 2) that when the wrist is hyperextended the depression between the tendon of the palmaris longus muscle and the tendon of the flexor carpi ulnaris muscle will be replaced by a bulge. This prominence is formed by the musculotendinous junction of the superficial and deep flexors of the four fingers.

The proximal end of the severed tendon in a digit often retracts into the hand. Familiarity with structures in the wrist is important in locating these retracted tendons. The three key tendons to be found at the wrist are important landmarks in locating these retracted tendons.

That this type of injury is encountered in other than large hand injury centers is demonstrated by a series of 108 patients treated at our hospital from 1945 through 1954. These patients incurred injuries to 287 flexor tendons. In 58 cases the three key tendons at the wrist were severed. The superficial flexor tendons of the digits were involved 106 times, while the deep digital flexors were injured only 84 times. Nine ulnar nerves at the wrist were injured, and seven median nerves at this level were severed. Twenty-one patients incurred injuries to the long flexor of the thumb.

SUMMARY

Injuries to the flexor surface of the wrist frequently sever tendons which cannot be demonstrated by any function test. A method of reviewing the topographic anatomy on one's own wrist is presented.

THE SURGEON'S LIBRARY

Reviews of New Books

ARTICLES ON BONE PATHOLOGY and orthopedic surgery written by members of the staff of the Florence Medical School and of other Italian Universities are included in the volume compiled by O. Scaglietti.[1]

J. Fineschi contributed a paper on osteogenic-osteolytic sarcoma with excellent color photomicrographs. The 10 cases of osteolytic-osteogenic sarcoma reported were more undifferentiated and more malignant than those of sclerosing-osteogenic sarcoma.

A statistical study of 467 metastatic bone tumors by Ricci showed that in 40 per cent the primary tumor could not be found. This may be due to the fact that primary tumors are very small and remain latent, whereas the bone metastases thrive.

Scaglietti discusses vascular lesions in fractures of the extremities. The treatment of Volkmann's contracture is designed to overcome the retraction of the involved muscles by detaching their proximal insertions from the humeral epicondyles, forearm bones, and interosseous membrane. The circulation is improved by sectioning longitudinally the forearm fascia. This is followed by tenolysis and neurolysis.

Calandriello in an anatomic study of 87 dorsal spines found disc protrusions in 8 cases.

A discussion by Catalano and Grassi on abduction fractures of the femoral neck emphasizes the fact that although the fractures healed readily the late results were poor, because of late aseptic necrosis in 60 per cent of the cases. The authors believe that conservative treatment of abduction fractures with marked displacement in valgus of the neck is inadequate, and they advise the reduction of these fractures so as to reconstitute the normal anatomy. Reduction is followed by internal fixation.

Intertrochanteric fractures are treated more successfully by conservative means than by surgery, according to Ducci and Giacci.

Monesi and Laus report on leg muscle biopsies in 10 cases with muscle atrophy due to herniation of the intervertebral disc. They found that the innervation in the affected area is not uniform and shows different characteristics in different patients. The muscles involved at first show simple atrophy and after 1 year undergo progressive degeneration. They are finally replaced by fibrous and fat tissue.

Mangini reports on 8 cases of stenosing tenosynovitis of the long flexor of the thumb in babies. In all cases, healing occurred spontaneously. When it is possible to extend the phalanx either actively or passively, the author immobilizes the distal phalanx in extension for 2 to 3 weeks if possible. Operation is not considered unless a long time has passed without spontaneous remission.

A review by Callandriello of hip arthroplasties done in the Orthopedic Institute in Florence shows rather poor late results. Vitallium cup arthroplasties seem to have done a little better than the stem prostheses. Results were acceptable in less than 50 per cent of the cases. The author believes that hip arthroplasty should be reserved for exceptional cases, particularly for very old people with neck fractures or in cases of bilateral ankylosis of the hip.

At the end of each article there is a short English résumé for readers not familiar with the Italian language. A very complete bibliography on orthopedic surgery and related subjects published in 1954 comprises the final one-third of the book.

—*I. V. Ponseti.*

THE VOLUME, *Der varikoese Symptomen-Komplex*,[2] is written by Friedrich Pirner, an associate member of the Munich University Hospital. It is the outgrowth of his profound knowledge and great experience in this special field. It includes also a summary of the world literature, starting with Hippocrates (470-371 B.C.).

In the first part, Pirner discusses the general concept of varicose veins and their consequences and complications. After a most interesting historical survey, he describes the etiology and symptoms. Details of the anatomy are given with numerous illustrations and tables, followed by descriptions of the physiology and pathology. The chapter dealing with diagnosis demonstrates the author's extensive experience in this field.

The subject of therapy is divided into three parts: conservative therapy, treatment by injections, and operative treatment.

The second part of the book is devoted to diagnostic pitfalls and therapeutic errors with their dangerous complications. The latter are again divided into

[1]ARCHIVIO "PUTTI" DI CHIRURGIA DEGLI ORGANI DI MOVIMENTO. Bibliografia year 1954. Vol. VIII. Directed by O. Scaglietti. Edited by L. Gui. 233 pages, illustrated. Firenze: Edizone Scientifiche Dell "Institito Ortopedico Toscano," 1957.

[2]DER VARIKOESE SYMPTOMEN-KOMPLEX; MIT SEINEN FOLGEN UND NACHKRANKHEITEN UNTER BESONDERER BERUECKSICHTIGUNG DER FEHLERQUELLEN IN DIAGNOSTIK UND THERAPIE. By Priv. Doz. Friedrich Pirner. 267 pages, 82 illustrations. DM 41. Stuttgart: Ferdinand Enke, 1957.

complications of the three groups just mentioned. This part of the volume is well illustrated and includes photomicrographs and tables, which underline the explanations given in a helpful manner. An interesting chapter lists the different operations and their complications. Not only Pirner's statistics, but others, especially those from the Anglo-American literature are considered in detail.

This book is an excellent compendium, in part because of its detailed index and alphabetical list of authors. Since the author considers not only his own large experience, but also statistics from world literature, his conclusions as to treatment may be used as a reliable guide. —*Frank Lichtenheld.*

A COMPILATION of 18 lectures presented by 17 speakers at an extension course given at the Women's Clinic of the Free University of Berlin is presented in the volume entitled *Frueherkennung und Behandlung des weiblechen Genitalcarcinoms.*[3] The speakers were not all gynecologists. Some were internists, general surgeons, cytologists, and specialists in other fields. The subject discussed was genital carcinoma and included the cervix, the corpus, the vagina, the ovaries, and the vulva. Those who spoke on early recognition of genital cancer emphasized colposcopy, biopsy, curettage, and of course, cytology. Treatment of carcinoma of the cervix included discussions of the vaginal radical operation, the Wertheim operation, and radiation therapy. For carcinoma of the corpus, ovaries, vagina, and vulva, both the advantages and dangers of surgery and irradiation were presented. There were also talks on the recognition and treatment of postoperative complications and the therapy of postoperative ureter and bladder fistulas. The 46 illustrations are clear and instructive, and 16 of them are in color.

There is nothing new in the book, but it is an excellent review of the entire subject of genital carcinoma in women. —*J. P. Greenhill.*

THE MONOGRAPH, *Pain in Gynecology,*[4] is the outgrowth of lectures on gynecology. It is intended to be of practical import. Pain of gynecologic origin may arise from a variety of foci. An approach to the problem is made by reviewing the anatomic and physiologic bases on which such distress depends as well as the pathways through which the pain travels. Psychic factors receive the emphasis which they properly deserve.

The book is made up of 7 chapters, each of approximately 20 pages. The chapters on abdominopelvic and on shoulder referred pain were written by E. Molinero; the chapter on treatment by E. Gil Vernet. The senior author contributed the other chapters.

The monograph is well organized and its practical approach should be helpful to young gynecologic specialists. —*Stephen A. Zieman.*

[3]FRUEHERKENNUNG UND BEHANDLUNG DES WEIBLICHEN GENITALCARCINOMS. Edited by Prof. Dr. F. v. Mikulicz-Radecki. With 17 contributors. 182 pages, 46 illustrations, 16 in color. Stuttgart: Ferdinand Enke, 1957.

[4]EL DOLOR EN GINECOLOGIA. By Manuel Usandizaga, Emilio Gil Vernet, and Emilio Molinero. Barcelona: Vergara Editorial, S. A.

THE SENIOR AUTHOR of the work *Traitement chirurgical de la recto-colite ulcero-hemorrogique*[5] is professor in the surgical clinic of the University of Lille Faculty of Medicine. The junior author is instructor in the same surgical clinic. The disease process they write about is defined as "hemorrhagic rectocolitis," which is said to be analogous to the English and American term, "ulcerative colitis." To be more specific, the authors say they accept the following description by Auguste, Paris, and Tacquet, made in 1935: "A serious disease of long duration, affecting part or all of the colon, predominantly on the surface of that structure, manifesting itself by a dysenteriform syndrome which most often develops in successive bouts and which produces a profound alteration of the general status and frequently may end by death of the patient." The authors are aware that some writers regard hemorrhagic rectocolitis and ulcerative colitis as two distinct entities, but say that since in each case the clinical symptoms, development of the disease, and the therapeutic indications are the same, they are willing, provisorily, to regard the pathologic manifestation of both conditions as "part of the same nosologic entity." They add that the incidence and severity of the disease seem to be increasing in France.

Professors Delannoy and Martinot point out that although the contributions of English and American authorities to the problem are considerable, their book is based on their own experience, "one of the most important in this country." They consider surgical forms of the disease, acute and chronic, and the complications thereof; such measures as appendicostomy, cecostomy, colostomy, ileostomy, bilateral vagotomy, resection of the autonomic pelvic nervous system, total colectomy, and coloproctectomy. They devote a chapter to their own technique of operation, and conclude that when the disease does not yield to a medical regime, surgical intervention is justified. They deprecate the value of appendicostomy, cecostomy, and various types of colostomy, and do not look with favor upon ileostomy alone. "It is total colectomy, justified by the clinical progression of the disease and especially by radiologic and operative findings, which will remain the operation of choice," the authors maintain. They declare that so far as anal ileostomy and re-establishment of the continuity of the bowel are concerned, "no solution of satisfactory certitude currently can be proposed and systematically carried out."

The volume has 26 illustrations, a bibliography, and an index of authors. —*L. A. Buie.*

THE LATEST PUBLICATION in a series having to do with the pathology and treatment of the vascular system and with certain parts of the autonomic nervous system by Georges Arnulf is entitled *Pathologie et chirurgie des carotides.*[6] The book is written at the suggestion of, and as a tribute to, the author's former chief, the late René Leriche.

It is divided into 5 sections: (1) anatomic and phys-

[5]TRAITEMENT CHIRURGICAL DE LA RECTO-COLITE ULCÉRO-HÉMORRAGIQUE. By E. Delannoy and M. Martinot. 120 pages, illustrated. 1.400 fr. Paris: Masson et Cie, 1957.

[6]PATHOLOGIE ET CHIRURGIE DES CAROTIDES. By Prof. Georges Arnulf. 544 pages, 154 illustrations. 6.800 fr. Paris: Masson et Cie, 1957.

iologic considerations of the carotid system; (2) the technique of carotid surgery (ligature, grafts, anastomosis, arteriectomy, intracarotid transfusion, arteriography); (3) the pathology of the carotids (malformations, wounds, thrombosis, aneurysms, fistulas); (4) the special pathology and surgery of the carotid body (with a review of its physiology, and the techniques of infiltration and surgical excision); (5) an extensive bibliography conveniently arranged with reference to the 4 preceding sections of the book.

Arnulf is well acquainted with the pertinent work of others in this special field, and he quotes those authors freely; however, he is not always in agreement with them and feels free to draw his conclusions mainly from his own extensive and carefully controlled observations. He is definitely oriented in his surgery by the physiologic and anatomic approaches, and it is reassuring to find that he is at the same time progressively investigative but conservative in drawing his conclusions. The discussion of the causes and results (such as thrombosis and cerebral vascular failure) after carotid ligation is particularly impressive, and he has much documented radiographic evidence to show that the re-establishment of normal cerebral circulation can be possible only after ligature of *one common carotid*, isolated, or in combination with the external carotid of that same side. Every other form and combination of carotid ligature produces a notable ischemia, permanent or even progressive.

The author apparently accepts the belief sometimes expressed that the carotid body secretes a hormone something like adrenalin in its actions, but he admits the lack of proof for this. He is inclined to think that infiltration of the carotid body in the treatment of epilepsy, certain mental states (depressions, acute anxiety), and shock is without much effect, but he recommends infiltration in the treatment of the syndrome of the hyperirritable carotid body when medical treatment has failed.

This volume is actually a source book on its subject, written in great detail yet so well organized that the reader may quickly find any particular topic. The book is well printed and strongly bound, with illustrations that are well chosen, and of a modest price.

—*John Martin.*

DURING THE PAST 25 YEARS, the authors of textbooks of pathology have followed ever more closely the fashion of writing systematic and encyclopedic "Hand Books." Indeed, if my memory still serves me well, it was W. G. MacCallum who last wrote a textbook of pathology based largely on personal experience and belief. This condition of affairs seems a pity, for the personal book has probably a better chance of striking fire in the beginning student and making the subject live for him than does the factual, impersonal one.

In the past decade 2 textbooks of pathology, both written by Englishmen, have broken with the handbook tradition and given highly individual accounts of the subject based primarily on personal experience. One of these, *General Pathology*,[7] is edited by Sir Howard Florey, Nobel laureate (penicillin) and Professor of Pathology at Oxford.

Florey first published his book in 1954 under the title *Lectures on General Pathology*. Now, in the second edition, he has changed the name to *General Pathology*. The book contains some of the lectures given at Oxford University to the medical students in the honors course. Fifteen eminent British experimental pathologists, not all of whom are from Oxford, have written the various chapters. The chief purpose of the lectures is to give an account of the various ways in which cells and tissues react to different kinds of injuries and the consequences of these reactions for the organism. Thus there are chapters on inflammation, necrosis and the degenerations, tumors, edema formation, healing, and cell growth and multiplication. The action of some of the common causes of disease, such as microorganisms, viruses, alterations of metabolism, and drugs are also considered as are the antigen-antibody reaction and hypersensitivity. In the new edition the chapters have been rearranged into a better sequence than in the first edition and chapters on thrombosis, metabolic changes following injury, atherosclerosis, and tumors have been added. Special pathology is not included.

The first edition was excellent and the second is even better. The authors have written succinct, lucid, and well balanced accounts of their assigned topics and have skillfully blended morphologic and experimental aspects. Each contributor has written from his own personal experience and interest. Questions are raised, thought is provoked, and new ways of looking at old matters are brought up in a most stimulating fashion. And to top it all, the prose of the authors is a delight to read and the illustrations please the eye. From all this you may gather that I think the book is first class—I hope you will, too.

—*William B. Wartman.*

THE EXCELLENT BOOK *Endocrine Pathology of the Ovary*[8] presents a coherent, well organized portrayal of a difficult subject, that of ovarian pathology with emphasis on the endocrinologic aspects.

Its scope includes a detailed introduction which begins with a presentation of the component cells of the gonads. A working knowledge of the anatomy and histology, is presupposed. Pertinent points in embryology are stressed. Sexual differentiation and sex hormone production are lucidly discussed at length, covering such details as its bisexual effects and hormone assay. The thorough definition of terms, such as estrinism and defeminization, used in the classification of hormone effects is most helpful.

The next topic is nonneoplastic abnormalities of the ovary with endocrine effect. This includes the Stein-Leventhal syndrome and hilar cell hyperplasia. An interesting observation by the authors is the frequency of cortical stromal hyperplasia and its associated lesions, i.e., focal lutein cell formation and cortical granulomas in cases of endometrial and breast cancers.

The classification of functioning ovarian tumors

[7] GENERAL PATHOLOGY; BASED ON LECTURES DELIVERED AT THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY, UNIVERSITY OF OXFORD. Edited by Sir Howard Florey. 2nd ed. 932 pages, illustrated. $16.00. Philadelphia and London: W. B. Saunders Co., 1958.

[8] ENDOCRINE PATHOLOGY OF THE OVARY. By John McLean Morris, M.D., and Robert E. Scully, M.D. 151 pages, 75 illustrations. $8.50. St. Louis: The C. V. Mosby Co., 1958.

into 5 divisions is based primarily on "broad morphologic categories," the reasons for which are cogently discussed and bring into proper perspective the role played by endocrinology. Each neoplastic entity is described systematically and succinctly in all its aspects. The final category, that of tumors with a "functioning stroma," is an intriguing one and accounts for such hormonal effects as have been frequently observed and "dismissed as coincidence."

With an attractive format, liberal use of descriptive case abstracts, excellent photomicrographs, and an extensive bibliography for each chapter, this 151 page book is altogether satisfying and comprehensive.

—M. C. Wheelock.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

OPERATIVE SURGERY. By Charles Rob, M.C., and Rodney Smith, M.S. Vol. VII. 273 pages, illustrated. Philadelphia: F. A. Davis Co., 1958.

PROGRESS IN NEUROBIOLOGY III. PSYCHOPHARMACOLOGY; PHARMACOLOGIC EFFECTS ON BEHAVIOR. Edited by Harry H. Pennes, M.D. 362 pages, 35 illustrations. $8.00. New York: Paul B. Heober, Inc., 1958.

RELIGIOUS DOCTRINE AND MEDICAL PRACTICE. By Richard Thomas Barton, M.D., F.A.C.S. 94 pages. $3.75. Springfield, Ill.: Charles C Thomas, 1958.

LEHRBUCH DER GYNAEKOLOGIE. By Prof. Dr. Med. Heinrich Martius. 426 pages, 454 illustrations. $11.85. Stuttgart: Georg Thieme Verlag, 1958.

WESEN UND BEDEUTUNG DER ENCHONDRALEN DYSOSTOSEN. By Dr. Med. Hans Mau. 219 pages, 82 illustrations. $6.40. Stuttgart: Georg Thieme Verlag, 1958.

A TEXT ON SYSTEMIC PATHOLOGY. Edited by Otto Saphir, M.D. Vol. I. 865 pages, illustrated. $32.00. New York and London: Grune & Stratton, 1958.

UNITED STATES ATOMIC ENERGY COMMISSION. PART I. BLOOD VOLUME DETERMINATIONS WITH RADIOACTIVE ISOTOPES AND OBSERVATIONS ON BLOOD VOLUME FLUCTUATIONS. PART II. INDEX OF CARDIAC CLEARANCE. March, 1958. AECU-3614. George Washington University, Washington D.C. 45 pages, 20 illustrations. $1.00. Available from the Office of Technical Services, Dept. of Commerce, Washington, D.C.

LES DECHIRURES OBSTÉTRICALES COMPLIQUÉES DU PÉRINÉE TRAITEMENT CHIRURGICAL. By René Musset, Marcel Cottrell, and Maurice Dubost. 120 pages, 19 illustrations. 1,400 fr. Paris: Masson et Cie, 1958.

CHIRURGIE D'EXÉRÈSE DANS LA TUBERCULOSE PULMONAIRE. By D. Honore. 216 pages, 11 illustrations. 3,300 fr. Paris: Masson et Cie, 1958.

CHIRURGIE INFANTILE D'URGENCE. By Marcel Fevre. 2nd ed. 718 pages, 201 illustrations. 8,000 fr. Paris: Masson et Cie, 1958.

SURGERY IN INFANCY AND CHILDHOOD; A HANDBOOK FOR MEDICAL STUDENTS AND GENERAL PRACTITIONERS. By Matthew White, M.B., Ch.B., F.R.C.S. (Edin.), and Wallace M. Dennison, M.D., F.R.C.S. (Edin.). 444 pages, 266 illustrations. $9.50. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: Williams & Wilkins Co., 1958.

CLEFT PALATE AND SPEECH. By Muriel E. Morley, M.Sc., F.C.S.T. 4th ed. 271 pages, 86 illustrations. $6.50. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: Williams & Wilkins, 1958.

A MANUAL ON CARDIAC RESUSCITATION. By Robert M. Hosler, M.D., F.A.C.S. 2nd ed. 208 pages, 17 illustrations. $5.50. Springfield, Ill.: Charles C Thomas, 1958.

MILESTONES IN MODERN SURGERY. By Alfred Hurwitz, M.D., and George A. Degenshein, M.D. 520 pages, illustrated. $15.00. New York: Paul B. Hoeber Inc., 1958.

PRINCIPLES OF GENERAL SURGICAL MANAGEMENT. By H. A. F. Dudley, assisted by B. C. Paton, I. F. MacLaren, I. B. Tait, and G. F. Murnaghan. Foreword by John Bruce. 203 pages, 58 illustrations. $6.50. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: Williams & Wilkins Co., 1958.

UNIVERSIDADE DO BRASIL INSTITUTO DE GINECOLOGIA. ARQUIVOS DE CLINICA GINECOLOGICA. Director Prof. Dr. Arnaldo de Moraes. Vol. VIII. 286 pages, illustrated. Rio De Janeiro: Paulo De Azevedo Ltda, 1955.

THE ACUTE ABDOMEN. By William Requarth, M.D. Foreword by Warren H. Cole, M.D. 2nd ed. 313 pages, 89 illustrations. Chicago: Year Book Publishers, Inc., 1958.

KLINISCHE CALORIMETRIE UND THERMOMETRIE, DIE THERMISCHEN MEBVERFAHREN ZUR REGISTRIERUNG DER HAUT-UND GEWEBEDURCHBLUTUNG AM MENSCHEN GRUNDLAGEN, TECHNIK METHODIK, ANWENDUNG IN KLINIK UND PRAXIS. By Dr. Helmut P. Kuemmerle. 112 pages, 52 illustrations. $4.30. Stuttgart: Georg Thieme Verlag, 1958.

ELECTROCARDIOGRAPHY. By Michael Bernreiter, M.D., F.A.C.P. 134 pages, 92 illustrations. $5.00. Philadelphia and Montreal: J. B. Lippincott Co., 1958.

ILLUSTRATED PREOPERATIVE AND POSTOPERATIVE CARE. By Philip Thorek, M.D., F.A.C.S., F.I.C.S. With drawings by Carl T. Linden. 98 pages, 59 illustrations. $5.00. Philadelphia and Montreal: J. B. Lippincott Co., 1958.

HOW TO LIVE WITH DIABETES. By Henry Dolger, M.D., and Bernard Seeman. 192 pages. $3.50. New York: W. W. Norton & Co., 1958.

THE PSYCHOLOGY OF MEDICAL PRACTICE. By Marc H. Hollender, M.D. 276 pages. $6.50. Philadelphia and London: W. B. Saunders Co., 1958.

PEDIATRIC SURGERY. By Orvar Swenson. Foreword by William E. Ladd. 750 pages, 980 illustrations. $20.00. New York: Appleton-Century-Crofts, Inc., 1958.

THE MEDICAL ASSISTANT; A GUIDEBOOK FOR THE NURSE, SECRETARY, AND TECHNICIAN IN THE DOCTOR'S OFFICE. By Miriam Bredow. 430 pages, illustrated. $7.50. New York, Toronto, London: McGraw-Hill Book Co., 1958.

MEDICAL ELECTRICAL EQUIPMENT; PRINCIPLES, INSTALLATION, OPERATION AND MAINTENANCE OF ELECTRICAL EQUIPMENT USED IN HOSPITALS AND CLINICS. Edited by Robert E. Molloy, M.B. 312 pages, 238 illustrations. $6.00. New York: Philosophical Library, Inc., 1958.

A MODERN PRACTICE OF OBSTETRICS. By D. M. Stern, M.B. and C. W. F. Burnett, M.D. (Lond.). 2nd ed. 258 pages, 141 illustrations. $9.00. London: Baillière, Tindall & Cox; Baltimore: The Williams & Wilkins Co., 1958.

DE RELATIE TUSSEN MILT EN GONADE; EXPERIMENTEEL ONDERZOEK BIJ RANA TEMPORARIA. By Antoon Gerard Joseph Van Sonderen. 80 pages, 17 illustrations. Amsterdam: Drukkerij H. J. Koersen En Zn., 1958.

THE AMERICAN COLLEGE OF SURGEONS

WILLIAM L. ESTES, JR., Bethlehem, Pennsylvania, *President*
NEWELL W. PHILPOTT, Montreal, Canada, *President-Elect*

PRELIMINARY PLANS FOR THE 44th CLINICAL CONGRESS THE CONRAD HILTON, CHICAGO, ILLINOIS OCTOBER 6 to 10, 1958

APPROXIMATELY 10,000 medical personnel from all over the world will be welcomed by Chicago, "Host City of the Nation," to the 44th annual Clinical Congress of the American College of Surgeons, October 6 to 10.

Clinical Congress forms for advance registration, hotel accommodations, Postgraduate Courses, and transportation may be obtained from The American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois. No registration fee is charged Fellows if dues are paid to December 31, 1957. If dues are not paid, the fee is $20.00. No registration fee is charged Initiates or members of the Candidate group. No fee is charged surgical residents provided a note of identification signed by their chief of surgery or hospital administrator accompanies the advance registration form. Non-Fellows pay a $20.00 fee. Members of the Federal Services pay $10.00. The Postgraduate Course fee is $5.00, payable by everyone taking the course. The official Registration Desks will observe the following hours: Sunday, October 5, 3:00 to 7:30 p.m.; Monday, October 6, 8:00 a.m. to 5:30 p.m.; Tuesday through Friday, 8:00 a.m. to 5:00 p.m.

In addition to the general scientific sessions hereinafter listed, the regular Clinical Congress evening and other functions will be presented as usual: The President's Evening, Monday, 8:30–10 p.m.; Convocation Evening, Friday, 8:30–10 p.m.; Annual Meeting—Board of Governors, Sunday, 9 a.m.–5 p.m.; Adjourned Meeting—Board of Governors, Wednesday, 1:30–5 p.m.; Annual Meeting of Fellows, Thursday, 3:45–5:15 p.m. These functions will be detailed in your Clinical Congress program handbook.

General Sessions

Monday, 10:00 a.m.—12 noon, Grand Ballroom, The Conrad Hilton

WILLIAM L. ESTES, JR., M.D., F.A.C.S., Bethlehem, Pennsylvania; *Presiding.*

EMERGENCIES IN POSTOPERATIVE CARE

Moderator: RICHARD L. VARCO, M.D., F.A.C.S., Minneapolis.

Collaborators: EUGENE M. BRICKER, M.D., F.A.C.S., St. Louis; B. EISEMAN, M.D., F.A.C.S., Denver; ALLAN D. MCKENZIE, M.D., F.A.C.S., Vancouver, British Columbia.

1:30—3:00 p.m., Grand Ballroom, The Conrad Hilton

PERIPHERAL ARTERIAL DISEASE

Moderator: OSCAR CREECH, JR., M.D., F.A.C.S., New Orleans.

Collaborators: WILEY F. BARKER, M.D., F.A.C.S., Los Angeles; RALPH A. DETERLING, JR., M.D., F.A.C.S., New York; J. C. LUKE, M.D., F.A.C.S., Montreal.

3:30—5:00 p.m., Grand Ballroom, The Conrad Hilton

INTESTINAL OBSTRUCTION

Moderator: RUDOLF J. NOER, M.D., F.A.C.S., Louisville.
Collaborators: ROBERT E. GROSS, M.D., F.A.C.S., Boston; CHARLES G. JOHNSTON, M.D., F.A.C.S., Detroit; CHAMP LYONS, M.D., F.A.C.S., Birmingham; OWEN H. WANGENSTEEN, M.D., F.A.C.S., Minneapolis.

Tuesday, 1:30—3:00 p.m., Grand Ballroom, The Conrad Hilton

SURGERY OF PELVIC CANCER

Moderator: HERBERT E. SCHMITZ, M.D., F.A.C.S., Chicago.
Collaborators: JUSTIN J. CORDONNIER, M.D., F.A.C.S., St. Louis; WARING G. COSBIE, M.D., Toronto; MILTON L. MCCALL, M.D., F.A.C.S., New Orleans; LANGDON PARSONS, M.D., F.A.C.S., Boston.

3:30—5:00 p.m., Grand Ballroom, The Conrad Hilton

SURGERY OF DUODENAL ULCER

Moderator: EDWARD S. JUDD, M.D., F.A.C.S., Rochester, Minnesota.
Collaborators: JOEL W. BAKER, M.D., F.A.C.S., Seattle; ROBERT C. HARRISON, M.D., F.A.C.S., Edmonton, Alberta; ROBERT M. ZOLLINGER, M.D., F.A.C.S., Columbus, Ohio.

2:00—5:00 p.m.

SYMPOSIUM ON TRAUMA (See page listing special symposia.)

Wednesday, 1:30—3:00 p.m., Grand Ballroom, The Conrad Hilton

INJURIES OF THE HAND

Moderator: JOSEPH H. BOYES, M.D., F.A.C.S., Los Angeles.
Collaborators: J. EDWARD FLYNN, M.D., F.A.C.S., Boston; STUART DOUGLAS GORDON, M.D., F.A.C.S., Toronto; VINTON E. SILER, M.D., F.A.C.S., Cincinnati.

2:00—2:40 p.m., Normandie Lounge, The Conrad Hilton

THE BAXTER LECTURE: GUNNAR THORSEN, M.D., Stockholm, Sweden.

2:45—5:00 p.m.

SYMPOSIUM ON CANCER (See page listing special symposia.)

3:30—5:00 p.m., Grand Ballroom, The Conrad Hilton

THE INTERVERTEBRAL DISK

Moderator: JAMES K. STACK, M.D., F.A.C.S., Chicago.
Collaborators: FRANK H. MAYFIELD, M.D., F.A.C.S., Cincinnati; JOHN RAAF, M.D., F.A.C.S., Portland, Oregon; ALEXANDER P. AITKEN, M.D., F.A.C.S., Brookline; MARK B. COVENTRY, M.D., F.A.C.S., Rochester, Minnesota.

Thursday, 1:30—3:00 p.m Grand Ballroom, The Conrad Hilton

SURGICAL SHOCK

Moderator: FRASER N. GURD. M D. F.A.C.S., Montreal.
Collaborators: JOHN M. HOWARD, M.D., F.A.C.S., Philadelphia; FRANCIS D. MOORE, M.D., F.A.C.S., Boston; ROBERT H. KENNEDY, M.D., F.A.C.S., New York.

3:00—3:45 p.m., Grand Ballroom, The Conrad Hilton

ORATION ON TRAUMA

The Immediate Care and Transportation of the Injured GEORGE J. CURRY, M.D., F.A.C.S., Flint, Michigan.

Friday, 8:30—11:30 a.m.

Exfoliative Cytology in the Differential Diagnosis of Malignancy of the Reproductive Organs. GEORGE L. WIED, M.D., Chicago.
Uterine Blood Flow and Its Implications. CHARLES H. HENDRICKS, M.D., F.A.C.S., Cleveland.
Ovulation Time. MELVIN R. COHEN, M.D., Chicago.
Ovarian Dysgenesis. SOMERS H. STURGIS, M.D., F.A.C.S., Boston.

9:00 a.m.—12 noon, Grand Ballroom, The Conrad Hilton

WHAT'S NEW IN SURGERY?

HARRIS B. SHUMACKER, JR., M.D., F.A.C.S., Indianapolis, *Presiding.*

Surgical Specialties

GYNECOLOGY AND OBSTETRICS

Monday, 1:30—3:00 p.m., Gold Room, Pick-Congress Hotel

PREVENTION OF ABORTION BY SURGICAL PROCEDURES

Moderator: ROBERT H. BARTER, M.D., F.A.C.S., Washington, D. C.
Collaborators: BERNARD J. PISANI, M.D., F.A.C.S., New York; H. L. RIVA, Col., M.C., U.S.A., F.A.C.S., Washington, D. C.; WILLIAM B. STROMME, M.D., F.A.C.S., Minneapolis.

3:30—5:00 p.m.

INDICATIONS FOR HYSTERECTOMY

Moderator: WALTER T. DANNREUTHER, M.D., F.A.C.S., New York.
Collaborators: L. A. CALKINS, M.D., Kansas City, Kansas; MICHAEL J. JORDAN, M.D., F.A.C.S., New York; NORMAN F. MILLER, M.D., F.A.C.S., Ann Arbor; E. STEWART TAYLOR, M.D., F.A.C.S., Denver.

Tuesday, 1:30—3:00 p.m.

OBSTETRICAL ANESTHESIA AND ANALGESIA

Moderator: RALPH A. REIS, M.D., F.A.C.S., Chicago.
Collaborators: RALPH E. CAMPBELL, M.D., F.A.C.S., Madison, Wisconsin; CHARLES S. STEVENSON, M.D., F.A.C.S., Detroit; H. HUDNALL WARE, JR., M.D., F.A.C.S., Richmond.

3:30—5:00 p.m.

LYMPHATIC PATHWAYS OF PELVIC CANCER

Moderators: JOE V. MEIGS, M.D., F.A.C.S., Boston.
Collaborators: BAYARD CARTER, M.D., Durham; JOHN B. GRAHAM, M.D., F.A.C.S., Buffalo; LANGDON PARSONS, M.D., F.A.C.S., Boston.

Wednesday, 1:30—3:00 p.m.

INDICATIONS FOR AND SELECTION OF FORCEPS FOR OBSTETRICAL DELIVERIES

Moderator: FRANK R. LOCK, M.D., F.A.C.S., Winston-Salem, North Carolina.
Collaborators: EDWARD H. DENNEN, M.D., F.A.C.S., New York; D. FRANK KALTREIDER, M.D., Baltimore; GEORGE B. MAUGHAN, M.D., F.A.C.S., Montreal.

3:30—5:00 p.m.

USE OF THE PROGESTERONE SYNTHETICS

Moderator: JOHN ROCK, M.D., F.A.C.S., Brookline.
Collaborators: CELSO-RAMÓN GARCÍA, M.D., Brookline; LUKE GILLESPIE, M.D., Brookline; CARL G. HELLER, M.D., Portland, Oregon; RICHARD L. LANDAU, M.D., Chicago; ANNA L. SOUTHAM, M.D., New York.

Friday, 1:30—3:00 p.m.

CURRENT KNOWLEDGE OF CAUSES OF CONGENITAL ANOMALIES

Moderator: ROBERT E. L. NESBIT, JR., M.D., Albany.
Collaborators: THEODORE H. INGALLS, M.D., Boston; PETER GRUENWALD, M.D., Jersey City; WILLIAM J. SCHULL, PH.D., Ann Arbor; SAMUEL B. KIRKWOOD, M.D., Boston.

3:15—4:45 p.m.

THE GYNECOLOGIST'S RESPONSIBILITY FOR DIAGNOSIS OF RECTAL AND BLADDER LESIONS

Moderator: FRANKLIN L. PAYNE, M.D., F.A.C.S., Philadelphia.
Collaborators: WILLIAM L. VALK, M.D., F.A.C.S., Kansas City, Kansas; CLAUDE E. WELCH, M.D., F.A.C.S., Boston; JOHN H. RIDLEY, M.D., F.A.C.S., Atlanta; ROGER B. SCOTT, M.D., Cleveland.

NEUROLOGIC SURGERY

Friday, 9:00—10:30 a.m.

NEUROSURGICAL PROBLEMS IN CEREBRAL PALSY

Moderator: RUSSELL MEYERS, M.D., F.A.C.S., Iowa City.

Collaborators: IRVING S. COOPER, M.D., F.A.C.S., New York; LYLE A. FRENCH, M.D., Minneapolis; WINTHROP M. PHELPS, M.D., F.A.C.S., Baltimore; A. EARL WALKER, M.D., F.A.C.S., Baltimore.

10:35 a.m.—12 noon.

METASTATIC TUMORS OF THE NERVOUS SYSTEM

Moderator: BRONSON S. RAY, M.D., F.A.C.S., New York.

Collaborators: EBEN ALEXANDER, JR., M.D., F.A.C.S., Winston-Salem, North Carolina; JOSEPH P. EVANS, M.D., F.A.C.S., Chicago; HERBERT PARSONS, M.D., New York.

2:00—5:00 p.m.

SYMPOSIUM IN NEUROLOGICAL SURGERY

EDGAR F. FINCHER, M.D., F.A.C.S., Atlanta, *Presiding.*

Brain Abscesses. H. THOMAS BALLANTINE, JR., M.D., F.A.C.S., Boston. Discussion by E. S. GURDJIAN, M.D., F.A.C.S., Detroit.

Lathyrism and Allied Subjects: Their Significance in Neurosurgery. WILLIAM J. GERMAN, M.D., New Haven, Connecticut. Discussion by A. EARL WALKER, M.D., F.A.C.S., Baltimore.

Management of Cervical Injuries. W. G. CRUTCHFIELD, M.D., Charlottesville, Virginia. Discussion by FRANK H. MAYFIELD, M.D., F.A.C.S., Cincinnati.

Present Evaluation of the Decompression of the Sensory Root in the Treatment of Trigeminal Neuralgia. W. JAMES GARDNER, M.D., F.A.C.S., Cleveland. Discussion by FRANCIS C. GRANT, M.D., F.A.C.S., Philadelphia.

Technique and Results of High Cervical Chordotomy. HENRY G. SCHWARTZ, M.D., F.A.C.S., St. Louis. Discussion by EDGAR A. KAHN, M.D., F.A.C.S., Ann Arbor.

ORTHOPEDIC SURGERY

Friday, 1:30—3:00 p.m.

FRACTURES OF THE ELBOW IN CHILDREN AND ADULTS

Moderator: T. CAMPBELL THOMPSON, M.D., F.A.C.S., New York.

Collaborators: WALTER P. BLOUNT, M.D., F.A.C.S., Milwaukee; JOHN J. FAHEY, M.D., F.A.C.S., Chicago; OLAV ROSTRUP, M.D., F.A.C.S., Edmonton, Alberta.

3:15—4:45 p.m.

MANAGEMENT OF OPEN FRACTURES

Moderator: FRANCIS J. COX, M.D., F.A.C.S., San Francisco.

Collaborators: JOSEPH R. SHAEFFER, Col., M.C., U.S.A., F.A.C.S., Washington, D. C.; JAMES D. HARDY, M.D., F.A.C.S., Jackson; FRED C. REYNOLDS, M.D., F.A.C.S., St. Louis; BENJAMIN E. OBLETZ, M.D., F.A.C.S., Buffalo.

PLASTIC SURGERY

Monday, 1:30—3:00 p.m., Florentine Room, Pick-Congress Hotel

FURTHER EXPERIENCES IN TISSUE TRANSPLANTATION

Moderator: SUMNER L. KOCH, M.D., F.A.C.S., Chicago.

Collaborators: W. A. ALTEMEIER, M.D., F.A.C.S., Cincinnati; R. E. BILLINGHAM, D.SC., Philadelphia; MINOT P. FRYER, M.D., F.A.C.S., St. Louis; GEORGE W. HYATT, Cdr., M.C., U.S.N., Bethesda.

3:30—5:00 p.m.

PLASTIC SURGICAL ASPECTS OF TRAUMA

Moderator: MILTON T. EDGERTON, JR., M.D., F.A.C.S., Baltimore.

Collaborators: JOHN L. BELL, M.D., F.A.C.S., Chicago; S. MILTON DUPERTUIS, M.D., F.A.C.S., Pittsburgh; HAL B. JENNINGS, JR., Lt. Col., M.C., U.S.A., F.A.C.S., Washington, D. C.

THORACIC SURGERY

Friday, 1:30—3:00 p.m.

THE PROBLEM OF INFECTIONS

Moderator: H. ROCKE ROBERTSON, M.D., F.A.C.S., Vancouver.

Collaborators: CHESTER W. HOWE, M.D., F.A.C.S., Newton Center, Massachusetts; W. H. SUTHERLAND, M.D., F.R.C.C., Vancouver, British Columbia; WILLIAM R. SANDUSKY, M.D., F.A.C.S., Charlottesville, Virginia.

3:15—4:45 p.m.

RECENT ADVANCES IN CARDIOVASCULAR SURGERY

Moderator: DONALD B. EFFLER, M.D., F.A.C.S., Cleveland.

Collaborators: HENRY T. BAHNSON, M.D., F.A.C.S., Baltimore; ALFRED W. HUMPHRIES, M.D., F.A.C.S., Cleveland; JOHN W. KIRKLAND, Rochester, Minnesota; C. WALTON LILLIHEI, M.D., F.A.C.S., Minneapolis.

UROLOGY

Monday, 3:30—5:00 p.m., Crystal Ballroom, Sheraton-Blackstone Hotel

METHODS OF APPROACH IN THE SURGERY OF THE KIDNEY AND ADRENALS

Moderator: VICTOR F. MARSHALL, M.D., F.A.C.S., New York.

Collaborators: JAMES M. CAMPBELL, M.D., F.A.C.S., Saskatoon, Saskatchewan; RICHARD CHUTE, M.D., F.A.C.S., Boston; HARRY M. SPENCE, M.D. F.A.C.S., Dallas.

Tuesday, 3:30—5:00 p.m.

DIAGNOSIS AND TREATMENT OF TESTICULAR TUMORS

Moderator: JOHN A. TAYLOR, M.D., F.A.C.S., New York.

Collaborators: F. K. MOSTOFI, M.D., F.C.A.P., Washington, D. C.; JOHN F. PATTON, Col., M.C., U.S.A., F.A.C.S., Washington, D. C.; S. F. WILLIAMS, Capt., M.C., U.S.N., Bethesda.

Wednesday, 1:30—3:00 p.m.

SURGICAL MANAGEMENT OF UROLITHIASIS

Moderator: FRANK HINMAN, JR., M.D., F.A.C.S., San Francisco.

Collaborators: MILO ELLIK, M.D., F.A.C.S., Long Beach, California; LESTER PERSKY, M.D., F.A.C.S., Cleveland; PETER L. SCARDINO, M.D., F.A.C.S., Savannah, Georgia.

Thursday

FORUM SESSION FOR UROLOGY

Friday, 1:30—3:00 p.m.

MANAGEMENT OF THE NEUROGENIC BLADDER

Moderator: GEORGE C. PRATHER, M.D., F.A.C.S., Brookline, Massachusetts.

Collaborators: FRANK C. HAMM, M.D., F.A.C.S., Brooklyn; DONALD R. SMITH, M.D., F.A.C.S., San Francisco; ERNEST BORS, M.D., F.A.C.S., Long Beach, California; HERBERT S. TALBOT, M.D., F.A.C.S., West Roxbury, Mass.

JOINT OPHTHALMOLOGY EVENING SESSION

(Of the Chicago Ophthalmological Society and the American College of Surgeons)

Wednesday, 8:00 p.m. (Preceded by a subscription dinner.)

J. V. CASSADAY, M.D., F.A.C.S., South Bend, President of the Chicago Ophthalmological Society; WILLIAM B. CLARK, M.D., F.A.C.S., New Orleans, Chairman of the Advisory Council for Ophthalmic Surgery of the American College of Surgeons, Co-Chairmen.

RECENT DEVELOPMENTS IN OPHTHALMIC SURGERY

Moderator: WILLIAM B. CLARK, M.D., F.A.C.S., New Orleans.

Collaborators: Orbit and Lids. LORAND V. JOHNSON, M.D., F.A.C.S., Cleveland. Corneal Surgery. R. TOWNLEY PATON, M.D., F.A.C.S., New York. Cataract and Glaucoma. F. BRUCE FRALICK, M.D., F.A.C.S., Ann Arbor, Surgery of the Retina. A. D. RUEDEMANN, M.D., F.A.C.S., Detroit.

JOINT OTOLARYNGOLOGY EVENING SESSION

(Of the Chicago Laryngological and Otological Society and the American College of Surgeons)

Wednesday, 8:00 p.m.

J. ALLAN WEISS, M.D., Chicago, President of the Chicago Laryngological and Otological Society; VICTOR GOODHILL, M.D., F.A.C.S., Los Angeles, Co-Chairmen.

SURGERY FOR DEAFNESS

Moderator: VICTOR GOODHILL, M.D., F.A.C.S., Los Angeles.

Collaborators: J. H. THOMAS RAMBO, M.D., New York; ROBERT HENNER, M.D., Chicago; EUGENE L. DERLACKI, M.D., Chicago; ARTHUR L. JUERS, M.D., Louisville; THEODORE E. WALSH, M.D., F.A.C.S., St. Louis.

Symposium On Trauma

Tuesday, 2:00—5:00 p.m., Williford Ballroom, The Conrad Hilton

PRESTON A. WADE, M.D., F.A.C.S., New York, Chairman, *Presiding.*

Trauma In Childhood. C. EVERETT KOOP, M.D., F.A.C.S., Philadelphia.

Postoperative Care of the Multiple Injury Patient. WAYNE W. GLAS, M.D., F.A.C.S., Eloise, Michigan.

The Problem of the Speeding Ambulance. SYDNEY N. LYTTLE, M.D., F.A.C.S., Flint, Michigan.

Present Status and Complications of Operative Treatment of Fractures. EDWIN FRENCH CAVE, M.D., F.A.C.S., Boston.

Observations in Vascular Dynamics During Hemorrhagic Shock. HERBERT J. ROBB, M.D., F.A.C.S., Detroit.

Symposium On Cancer

Wednesday, 2:45—5:00 p.m.

DANELY P. SLAUGHTER, M.D., F.A.C.S., Chicago, Chairman, *Presiding.*

Management of the Patient with Positive Vaginal Cell Examination. JOE V. MEIGS, M.D., F.A.C.S., Boston.

Current Status of Diagnosis and Treatment of Lung Cancer. O. T. CLAGETT, M.D., F.A.C.S., Rochester, Minn.

Current Status of Diagnosis and Treatment of Prostate Cancer. VINCENT J. O'CONOR, M.D., F.A.C.S., Chicago.

Present Status of Diagnosis and Treatment of Stomach Cancer. JAMES T. PRIESTLEY, M.D., F.A.C.S., Rochester, Minnesota.

Motion Picture Symposium On Spectacular Problems In Surgery

Wednesday, 7:30—10:00 p.m., Grand Ballroom, The Conrad Hilton

SERIES OF SHORT FILMS PERSONALLY NARRATED BY PARTICIPATING SURGEONS

EDWARD STARR JUDD, M.D., F.A.C.S., Rochester, Minnesota, *Presiding.*

Large Prolapsing Polypoid Carcinoma; Abdominoperineal Resection. JAMES D. HARDY, M.D., F.A.C.S., and HEBER C. ETHERIDGE, M.D., Jackson, Mississippi.

Ectopia Cordis. ELLIOTT S. HURWITT, M.D., F.A.C.S., New York.

Sacrococcygeal Meningocele. PATRICK H. HANLEY, M.D., F.A.C.S., New Orleans.

Wilms' Tumor. ROWENA SPENCER, M.D., New Orleans.

Replacement of Aneurysmal Femoral Homograft by Crimped Nylon Prosthesis. OTTO H. TRIPPEL, M.D., HAROLD LAUFMAN, M.D., F.A.C.S., and ROBERT P. HOHF, M.D., F.A.C.S., Chicago.

Giant Tumor of the Head; Sebaceous Epithelioma. ISIDORE COHN, JR., M.D., F.A.C.S., and HOWARD L. MARTIN, M.D., New Orleans.

Duplication Stomach. HUGH B. LYNN, M.D., F.A.C.S., Louisville.

Myelomeningocele of the Newborn. FREDERICK E. KREDEL, M.D., F.A.C.S., Charleston, South Carolina.

Surgical Repair of Anomalous Coronary Arteries and Arteriovenous Fistulas and Aneurysms. EGBERT H. FELL, M.D., F.A.C.S., MILTON WEINBERG, M.D., ARCHIE S. GORDON, M.D., F. R. JOHNSON, M.D., and EILEEN HECKEL, M.D., Chicago.

Carcinoma of Duodenum. STANLEY R. FRIESEN, M.D., F.A.C.S., Kansas City, Kansas.

Segmental Resection of Arteriovenous Fistula of the Lung. JOHANN L. EHRENHAFT, M.D., F.A.C.S., Iowa City.
Gallstone Ileus. JAMES D. HARDY, M.D., F.A.C.S., Jackson, Mississippi.
Ventricular Aneurysm Following Myocardial Infarction. DENTON A. COOLEY, M.D., F.A.C.S., Houston.
Trichobezoar. WALTMAN WALTERS, M.D., F.A.C.S., Rochester, Minnesota.
Coronary Endarterectomy for Angina Pectoris. WILLIAM P. LONGMIRE, JR., M.D., F.A.C.S., and JACK A. CANNON, M.D., F.A.C.S., Los Angeles.
Echinococcus Cyst of the Liver. EDWARD STARR JUDD, M.D., F.A.C.S., Rochester, Minnesota.

Symposium On Graduate Training In Surgery and the Surgical Specialties

Thursday, 1:30—3:00, Normandie Lounge, The Conrad Hilton

ROBERT M. ZOLLINGER, M.D., F.A.C.S., Columbus, Ohio, *Presiding.*
Compensation of Residents in Federal Services. JOHN C. NUNEMAKER, M.D., Chicago.

THE DISAPPEARING SERVICE PATIENT

Moderator: ROBERT M. ZOLLINGER, M.D., F.A.C.S., Columbus, Ohio.
Collaborators: STANLEY O. HOERR, M.D., F.A.C.S., Cleveland; HAROLD A. ZINTEL, M.D., F.A.C.S., New York; WARREN H. COLE, M.D., F.A.C.S., Chicago; LAWRENCE HOWE, Attorney, Chicago.

Television

Monday, 10:00 a.m.—12 noon, Williford Ballroom, The Conrad Hilton

Closure of Intra-atrial Defect. F. JOHN LEWIS, M.D., F.A.C.S., Chicago.
Moderator: OSCAR CREECH, JR., M.D., F.A.C.S., New Orleans.
Panel: HENRY T. BAHNSON, M.D., F.A.C.S., Baltimore; JOHANN L. EHRENHAFT, M.D., F.A.C.S., Iowa City; FRANK GERBODE, M.D., F.A.C.S., San Francisco.

2:00—3:30 p.m.

Herniated Nucleus Pulposus. LOYAL DAVIS, M.D., F.A.C.S., Chicago.
Moderator: E. S. GURDJIAN, M.D., F.A.C.S., Detroit.
Panel: DANIEL RUGE, M.D., F.A.C.S., Chicago; JOHN E. SCARFF, M.D., F.A.C.S., New York; FRANK E. STINCHFIELD, M.D., F.A.C.S., New York.

3:30—5:00 p.m.

Surgery of the Foot. EMIL D. W. HAUSER, M.D., F.A.C.S., Chicago; WILLIAM A. LARMON, M.D., F.A.C.S., Chicago; JAMES K. STACK, M.D., F.A.C.S., Chicago.
Moderator: HAROLD B. BOYD, M.D., F.A.C.S., Memphis.
Panel: CRAWFORD J. CAMPBELL, M.D., F.A.C.S., New York; FRANCIS M. MCKEEVER, M.D., F.A.C.S., Los Angeles; JAMES S. MILES, M.D., F.A.C.S., Denver.

Tuesday, 10:00 a.m.—12 noon, Williford Ballroom, The Conrad Hilton

Pneumonectomy. THOMAS W. SHIELDS, M.D., Chicago.
Moderator: WILLIAM E. ADAMS, M.D., F.A.C.S., Chicago.
Panel: THOMAS H. BURFORD, M.D., F.A.C.S., St. Louis; CAMERON HAIGHT, M.D., F.A.C.S., Ann Arbor; JULIAN JOHNSON, M.D., F.A.C.S., Philadelphia.

2:00—3:30 p.m.

Flexor Tendon Graft. SUMNER L. KOCH, M.D., F.A.C.S., Chicago; WILLIAM B. STROMBERG, M.D., F.A.C.S., Chicago.
Moderator: JOSEPH H. BOYES, M.D., F.A.C.S., Los Angeles.
Panel: S. BENJAMIN FOWLER, M.D., Nashville; GEORGE S. PHALEN, M.D., F.A.C.S., Cleveland.

3:30—5:00 p.m.

Excision of Palmar Fascia for Dupuytren's Contracture. MICHAEL L. MASON, M.D., F.A.C.S., Chicago; JOHN L. BELL, M.D., F.A.C.S., Chicago.
Moderator: VINTON E. SILER, M.D., F.A.C.S., Cincinnati.
Panel: MORRIS J. DIRSTINE, M.D., F.A.C.S., Seattle; STUART DOUGLAS GORDON, M.D., F.A.C.S., Toronto.

Wednesday, 10:00—11:00 a.m.

Inguinal Hernioplasty. W. HARRISON MEHN, M.D., F.A.C.S., Chicago.

11:00 a.m.—12 noon

Ventral Hernioplasty. HAROLD L. METHOD, M.D., F.A.C.S., Chicago.
Moderator: HENRY N. HARKINS, M.D., F.A.C.S., Seattle.
Panel: EUGENE M. BRICKER, M.D., F.A.C.S., St. Louis; CHESTER B. MCVAY, M.D., F.A.C.S., Yankton, South Dakota; WILLIAM H. SNYDER, JR., M.D., F.A.C.S., Los Angeles.

2:00—3:30 p.m.

Radical Mastectomy. WALTER W. CARROLL, M.D., F.A.C.S., Chicago.
Moderator: J. GARROTT ALLEN, M.D., F.A.C.S., Chicago.
Panel: W. EMORY BURNETT, M.D., F.A.C.S., Philadelphia; CLAUDE E. WELCH, M.D., F.A.C.S., Boston.

3:30—5:00 p.m.

Hypophysectomy. NICHOLAS WETZEL, M.D., F.A.C.S., Chicago.
Moderator: THEODORE B. RASMUSSEN, M.D., Montreal.
Panel: WILLIAM M. S. IRONSIDE, M.D., Chicago; BRONSON S. RAY, M.D., F.A.C.S., New York.

Thursday, 10:00 a.m.—12 noon

Neck Dissection with Hemimandibulectomy. ORION H. STUTEVILLE, M.D., F.A.C.S., Chicago.
Moderator: DWIGHT E. CLARK, M.D., F.A.C.S., Chicago.
Panel: MINOT P. FRYER, M.D., F.A.C.S., St. Louis; WILLIAM F. MACFEE, M.D., F.A.C.S., New York; DANELY P. SLAUGHTER, M.D., F.A.C.S., Chicago.

2:00—3:15 p.m.

Diagnostic Gynecologic Problems. STUART ABEL, M.D., F.A.C.S., Chicago; EDWIN J. DECOSTA, M.D., F.A.C.S., Chicago; JOHN W. HUFFMAN, M.D., F.A.C.S., Chicago.
Moderator: JOHN I. BREWER, M.D., F.A.C.S., Chicago.
Panel: JOHN C. BURCH, M.D., F.A.C.S., Nashville, RALPH E. CAMPBELL, M.D., F.A.C.S., Madison, Wisconsin; HOWARD ULFELDER, M.D., F.A.C.S., Boston.

3:15—4:00 p.m.

Anal Contracture. THOMAS J. MERAR, M.D., F.A.C.S., Chicago.
Moderator: ORVAR SWENSON, M.D., F.A.C.S., Boston.
Panel: MARK M. RAVITCH, M.D., F.A.C.S., Baltimore; RUBERT B. TURNBULL, JR., M.D., F.A.C.S., Cleveland.

Friday, 10:00—11:00 a.m.

Cesarean Section with Gastric Aspiration. RALPH A. REIS, M.D., F.A.C.S., Chicago.
Moderator: BERNARD J. PISANI, M.D., F.A.C.S., New York.
Panel: WILLARD ALLEN, M.D., St. Louis; GEORGE F. MELODY, M.D., F.A.C.S., San Francisco; EUGENE L. SLOTKOWSKI, M.D., Chicago.

11:00 a.m.—12 noon

Vaginal Hysterectomy. JOHN I. BREWER, M.D., F.A.C.S., Chicago.
Moderator: JOE V. MEIGS, M.D., F.A.C.S., Boston.
Panel: LANGDON PARSONS, M.D., F.A.C.S., Boston; NEWELL W. PHILPOTT, M.D., F.A.C.S., Montreal; HERBERT E. SCHMITZ, M.D., F.A.C.S., Chicago.

2:00—3:30 p.m.

Femoral Artery Bypass Graft. HAROLD LAUFMAN, M.D., F.A.C.S., Chicago.
Moderator: H. WILLIAM SCOTT, JR., M.D., F.A.C.S., Nashville.
Panel: JERE W. LORD, JR., M.D., F.A.C.S., New York; D. EMERICK SZILAGYI, M.D., F.A.C.S., Detroit.

3:30—5:00 p.m.

Cholecystectomy with Cholangiogram. B. FRANKLIN LOUNSBURY, M.D., F.A.C.S., Chicago.
Moderator: FRANK GLENN, M.D., F.A.C.S., New York.
Panel: ROBERT J. COFFEY, M.D., F.A.C.S., Washington, D. C.; WILLIAM BURKE HUTCHINSON, M.D., F.A.C.S., Seattle; I. S. RAVDIN, M.D., F.A.C.S., Philadelphia.

Ciné Clinics

Monday, 1:30—5:00 p.m., Eighth Street Theatre

GEORGE H. HUMPHRIES II, M.D., F.A.C.S., New York, *Presiding.*

Anomalies of the Heart. GEORGE H. HUMPHRIES II.
Open Heart Surgery. WILLIAM H. MULLER, JR., M.D., F.A.C.S., Charlottesville, Virginia.
Intra-atrial Septal Defects. F. JOHN LEWIS, M.D., F.A.C.S., Chicago.
Median Sternotomy and Elective Cardiac Arrest in Open Heart Surgery. FRANK L. GERBODE, M.D., F.A.C.S., San Francisco.
Pericardiectomy. HARRIS B. SHUMACKER, JR., M.D., F.A.C.S, Indianapolis.
Coronary Endarterectomy. WILLIAM P. LONGMIRE, JR., M.D., F.A.C.S., Los Angeles.
Occlusive Disease of Aorta. MICHAEL E. DEBAKEY, M.D., F.A.C.S., Houston.

Tuesday, 8:30 a.m.—12:30 p.m., Grand Ballroom, The Conrad Hilton

GEORGE G. FINNEY, M.D., F.A.C.S., Baltimore, *Presiding.*

Transabdominal Adrenalectomy for Endocrine Disease. EDWIN H. ELLISON, M.D., F.A.C.S., Columbus, Ohio.
Neglected Surgical Lesions. HUGH E. STEPHENSON, JR., M.D., F.A.C.S., Columbia, Missouri.
Acute Gallbladder Disease. ALLEN M. BOYDEN, M.D., F.A.C.S., Portland, Oregon.
Femoral Hernia. CLARENCE DENNIS, M.D., F.A.C.S., Brooklyn.
Staphylococcal Infections in Surgery. H. ROCKE ROBERTSON, M.D., F.A.C.S., Vancouver, British Columbia.
Fibroids of the Uterus. WILLARD H. PARSONS, M.D., F.A.C.S., Vicksburg, Mississippi.
Gastrectomy. DIGBY CHAMBERLAIN, M.B., CH.M., F.A.C.S.(Hon.), F.R.C.S.(Eng.). Leeds, England.

Wednesday, 8:30 a.m.—12:30 p.m., Grand Ballroom, The Conrad Hilton

ROBERT M. ZOLLINGER, M.D., F.A.C.S., Columbus, Ohio, *Presiding.*

Surgical Treatment of Prolapse of Rectum. WILLIAM A. ALTEMEIER, M.D., F.A.C.S., Cincinnati.
Meconium Ileus. DONALD M. GLOVER, M.D., F.A.C.S., Cleveland.
Duodenal Obstruction in Infancy. RUDOLF J. NOER, M.D., F.A.C.S., and HUGH B. LYNN, M.D., F.A.C.S., Louisville.
Presentation of Plaques to 1957 Ciné Clinic Participants.

CINÉ PANEL ON SURGERY OF THE LARGE INTESTINE

Carcinoma of the Colon. JOHN M. WAUGH, M.D., F.A.C.S., Rochester, Minnesota.
Volvulus. HARWELL WILSON, M.D., F.A.C.S., Memphis.
Ulcerative Colitis. HOWARD A. PATTERSON, M.D., F.A.C.S., New York.
Diverticulitis. R. KENNEDY GILCHRIST, M.D., F.A.C.S., Chicago.
Familial Polyposis. WALTER G. MADDOCK, M.D., F.A.C.S., Chicago.
Perforating Carcinoma of the Cecum and Colon. WARREN H. COLE, M.D., F.A.C.S., Chicago.
Polyps of the Colon. WILLIAM D. HOLDEN, M.D., F.A.C.S., Cleveland.
Various Lesions Seen on Proctoscopy. RAYMOND J. JACKMAN, M.D., Rochester, Minnesota.

Thursday, 8:30 a.m.—12:30 p.m., Grand Ballroom, The Conrad Hilton

HAROLD D. HARVEY, M.D., F.A.C.S., New York, *Presiding.*

Coarctation of the Aorta. EARLE B. MAHONEY, M.D., F.A.C.S., Rochester, New York.
Myasthenia Gravis, Diagnosis and Treatment by Thymectomy. MERLE M. MUSSELMAN, M.D., F.A.C.S., Omaha.
Splenectomy. FRANK F. ALLBRITTEN, JR., M.D., F.A.C.S., Kansas City, Kansas.
Hernia Repair with Nylon Mesh. JOHN R. PAINE, M.D., F.A.C.S., Buffalo.
Carcinoma of the Vulva. HOWARD ULFELDER, M.D., F.A.C.S., Boston.
Gastrectomy. WALTMAN WALTERS, M.D., F.A.C.S., and WILLIAM H. RE MINE, M.D., F.A.C.S., Rochester, Minnesota.
Thyroidectomy. RICHARD B. CATTELL, M.D., F.A.C.S., Boston.

Postgraduate Courses

PREOPERATIVE AND POSTOPERATIVE CARE

DAVID V. HABIF, M.D., F.A.C.S., New York, *Chairman.*

Tuesday, 8:30—11:30 a.m., American College of Surgeons Auditorium

FLUIDS AND ELECTROLYTES

FRANCIS D. MOORE, M.D., F.A.C.S., Boston, *Moderator.*

Normal Body Composition. JOHN M. BEAL, M.D., F.A.C.S., New York.

Body Composition Disorders in Surgical Patients. JAMES D. MCMURREY, M.D., Houston.
The Control of Body Composition by Renal Function. PARKER VANAMEE, M.D., New York.
Reliability and Significance of Laboratory Tests in Surgical Patients. HENRY T. RANDALL, M.D., F.A.C.S., New York.
Degenerative Change in Organ Function (of Brain and Circulation) Due to Fluid and Electrolyte Disorders. FRANCIS D. MOORE, M.D., F.A.C.S., Boston.
Case Analysis Clinic: ROBERT E. L. BERRY, *Presiding*, FRANCIS D. MOORE, HENRY T. RANDALL, JOHN M. BEAL, HAROLD G. BARKER, JAMES D. MCMURREY, PARKER VANAMEE.

Wednesday, 8:30—11:30 a.m.

NUTRITION FOR THE SURGICAL PATIENT

HENRY T. RANDALL, M.D., F.A.C.S., New York, *Moderator*.
Alimentary Route—Nasogastric Tube, Gastrostomy, Jejunostomy—Indications, Formulae, Management. EDWIN H. ELLISON, M.D., F.A.C.S., Milwaukee.
Intravenous Route—What, How Much, When?. HORACE J. MCCORKLE, M.D., F.A.C.S., San Francisco.
The Use of Testosterone Proprionate and Other Anabolic Hormones in Surgical Nutrition. WILLIAM E. ABBOTT, M.D., F.A.C.S., Cleveland.
Management of the Nutritionally Depleted Patient Undergoing Major Surgery. STANLEY M. LEVENSON, M.D., Washington, D. C.
Nutritional Support of the Burned Patient. CURTIS P. ARTZ, M.D., F.A.C.S., Jackson, Mississippi.
Present Status of Fat Emulsions for Intravenous Use. WILLIAM R. WADDELL, M.D., F.A.C.S., Boston.
Feeding Problems Following Gastric Surgery. WALTER LAWRENCE, JR., M.D., New York.
Case Analysis Clinic: WILLIAM E. ABBOTT, *Presiding*. HORACE J. MCCORKLE, CURTIZ P. ARTZ, ROBERT E. L. BERRY, EDWIN H. ELLISON, STANLEY M. LEVENSON, WILLIAM R. WADDELL.

Thursday, 8:30—11:30 a.m.

ENDOCRINOLOGY AND THE SURGICAL PATIENT

JAMES D. HARDY, M.D., F.A.C.S., Jackson, Mississippi, *Moderator*.
Physiology of the Adrenal Gland—Normal and in Relation to Trauma. DAVID M. HUME, M.D., F.A.C.S., Richmond, Virginia.
Assessment of Adrenal Function. JOSEPH W. JAILER, M.D., New York.
Preoperative and Postoperative Care of Patients Needing Adrenal Steroid Supplementation. JAMES D. HARDY, M.D., F.A.C.S., Jackson.
Aldosterone and Sodium Metabolism in Trauma. BERNARD ZIMMERMANN, M.D., F.A.C.S., Minneapolis.
Preoperative and Postoperative Management of Patients with Pheochromocytoma. VICTOR RICHARDS, M.D., F.A.C.S., San Francisco.
Preoperative and Postoperative Management of Patients with Hyperparathyroidism. LEON GOLDMAN, M.D., F.A.C.S., San Francisco.
Case Analysis Clinic. DAVID M. HUME, *Presiding*. JAMES D. HARDY, LEON GOLDMAN, VICTOR RICHARDS, BERNARD ZIMMERMANN, JOSEPH W. JAILER.

Friday, 8:30—11:30 a.m.

SPECIAL PROBLEMS IN SURGICAL PATIENTS

DAVID V. HABIF, M.D., F.A.C.S., New York, *Moderator*.
Prophylactic Antibiotics in Elective Surgery. EDWIN J. PULASKI, Lt. Col., U.S.A., M.D., F.A.C.S., San Francisco.
The Problem of Antibiotic Resistant Hospital Acquired Hemolytic Staphylococcus Aureus. H. TAYLOR CASWELL, M.D., F.A.C.S., Philadelphia.
Preoperative and Postoperative Management of Patients with Chronic Pulmonary Fibrosis, Emphysema and Asthma. GUSTAV J. BECK, M.D., New York.
Spontaneous Hemostasis, Coagulation, and Hemorraghic States. WILLIAM D. HOLDEN, M.D., F.A.C.S., Cleveland.
Surgical Shock as Seen Clinically Today: the Blood Volume, Myocardial Function, and Supportive Drugs. FRANCIS D. MOORE, M.D., F.A.C.S., Boston.
Case Analysis Clinic. HENRY T. RANDALL, *Presiding*. FRANCIS D. MOORE, CHAMP LYONS, ROBERT M. ZOLLINGER, EDWIN J. PULASKI, H. TAYLOR CASWELL.

GASTROINTESTINAL TRACT

JOHN M. WAUGH, M.D., F.A.C.S., Rochester, Minnesota, *Chairman.*

Tuesday, 8:30—11:30 a.m., Eleventh Street Theatre

ESOPHAGUS AND STOMACH

JOHN M. DORSEY, M.D., F.A.C.S., Evanston, *Moderator.*

Tracheo-esophageal Fistula. N. LOGAN LEVEN, M.D., F.A.C.S., St. Paul, Minnesota.
Benign Tumors of the Esophagus. PHILIP E. BERNATZ, M.D., F.A.C.S., Rochester, Minnesota.
Bleeding Esophageal Varices and their Management. C. STUART WELCH, M.D., F.A.C.S., Albany, New York.
Perforation of the Esophagus. JOHN M. DORSEY, M.D., F.A.C.S., Evanston, Illinois.
The Treatment of Acutely Perforating Peptic Ulcer. HENRY N. HARKINGS, F.A.C.S., M.D., Seattle.
The Surgical Physiology and Treatment of Peptic Ulcer. LESTER R. DRAGSTEDT, M.D., F.A.C.S., Chicago.
The Management of Gastric Malignancy. WILLIAM P. LONGMIRE, JR., M.D., F.A.C.S., Los Angeles.
Question and Answer Period.

Wednesday, 8:30—11:30 a.m.

SMALL INTESTINE

R. KENNEDY GILCHRIST, M.D., F.A.C.S., *Moderator.*

Malrotation, its Diagnosis and Treatment. WILLIAM B. KIESEWETTER, M.D., F.A.C.S., Pittsburgh.
Early Operation for Small Bowel Obstruction. WALTER G. MADDOCK, M.D., F.A.C.S., Chicago.
The Treatment of Diverticula of the Small Intestine. RICHARD B. CATTELL, M.D., F.A.C.S., Boston.
Regional Enteritis; Medical Aspects. CLIFFORD J. BARBORKA, M.D., F.A.C.P., Chicago.
The Surgical Management of Regional Enteritis. R. KENNEDY GILCHRIST, M.D., F.A.C.S., Chicago.
Clinical Aspects and Management of Functioning Carcinoid Tumors. WILLIAM G. SAUER, M.D., F.A.C.P., Rochester, Minnesota.
Surgical Aspects of Tumors of the Small Intestine. KENNETH E. LEMMER, M.D., F.A.C.S., Madison, Wisconsin.
Question and Answer Period.

Thursday, 8:30—11:30 a.m.

SURGERY OF THE COLON, RECTUM AND ANUS

W. A. ALTEMEIER, M.D., F.A.C.S., Cincinnati, *Moderator.*

New Trends in the Management of Diverticulitis. EDWARD S. JUDD, M.D., F.A.C.S., Rochester, Minnesota.
Volvulus of the Sigmoid. HARWELL WILSON, M.D., F.A.C.S., Memphis.
Ileostomy: Indications, Technique, and Care. RUPERT B. TURNBULL, JR., M.D., F.A.C.S., Cleveland.
Colostomy: Indications, Types, and Techniques. JOHN T. REYNOLDS, M.D., F.A.C.S., Chicago.
Fluid and Electrolyte Problems in Intestinal Surgery and Their Correction. CHAMP LYONS, M.D., F.A.C.S., Birmingham.
Pancolectomy, Subtotal Colectomy, or Anal Ileostomy for Ulcerative Colitis. MARK M. RAVITCH, M.D., F.A.C.S., Baltimore.
Treatment of Prolapse of the Rectum. W. A. ALTEMEIER, M.D., F.A.C.S., Cincinnati.
Imperforate Anus. ROBERT E. GROSS, M.D., F.A.C.S., Boston.

Friday, 8:30—11:30 a.m.

SURGERY OF THE COLON, RECTUM AND ANUS

EUGENE M. BRICKER, M.D., F.A.C.S., St. Louis, *Moderator.*

Antibiotics in Intestinal Surgery. ISIDORE COHN, JR., M.D., F.A.C.S., New Orleans.
The Indications for Total and Subtotal Colectomy in the Treatment of Cancer and Multiple Polyps of the Colon. ROBERT S. GRINNELL, M.D., F.A.C.S., New York.
Experiences with the Pull-Through Operation. JOHN C. TURNER, JR., M.D., Rochester, Minnesota.
The Management of Complications after the Miles Operation. JOSEPH A. BUCKWALTER, M.D., F.A.C.S., Iowa City.
Experiences with the "Second Look" Operation in Cancer of the Colon. STUART W. ARHELGER, M.D., F.A.C.S., Minneapolis.
The Treatment of Squamous Cell Epithelioma of the Anus. SAMUEL MCLANAHAN, M.D., F.A.C.S., Baltimore.
The Indications for and the Late Results of Pelvic Exenteration. EUGENE M. BRICKER, M.D., F.A.C.S., St. Louis.
Experiences with and Rationale of Chemotherapy in the Treatment of Cancer of the Colon. WARREN H. COLE, M.D., F.A.C.S., Chicago.

DISEASES OF THE LIVER, BILIARY TRACT, AND PANCREAS

WILLIAM D. HOLDEN, M.D., F.A.C.S., Cleveland, *Chairman.*

Tuesday, 8:30—11:30 a.m., Upper Tower, The Conrad Hilton

THE LIVER

WILLIAM D. HOLDEN, M.D., F.A.C.S., *Moderator.*

Evaluation of Hepatic Function. ROBERT M. ZOLLINGER, M.D., F.A.C.S., Columbus, Ohio.
Hepatoscan with Isotopes. JOHN P. STORAASLI, M.D., Cleveland.
Unusual Disorders Producing Jaundice: Cholangiolitic Hepatitis, Chlorpromazine Hepatitis, and Homologous Serum Jaundice. JOSEPH B. KIRSNER, M.D., F.A.C.P., Chicago.
Management of Hepatic Coma. B. EISEMAN, M.D., F.A.C.S., Denver.
Hepatic Resection. HARVEY R. BUTCHER, JR., M.D., F.A.C.S., St. Louis.
Management of Intrahepatic and Perihepatic Abscesses. ALTON OCHSNER, M.D., F.A.C.S., New Orleans.

Wednesday, 8:30—11:30 a.m.

BILIARY TRACT SURGERY

WILLIAM P. LONGMIRE, JR., M.D., F.A.C.S., Los Angeles, *Moderator.*

Pathogenesis of Acute Cholecystitis. WILLIAM D. HOLDEN, M.D., F.A.C.S., Cleveland.
Bacteriology of the Extrahepatic Biliary Tract. W. A. ALTEMEIER, M.D., F.A.C.S., Cincinnati.
Management of Acute Cholecystitis. STANLEY O. HOERR, M.D., F.A.C.S., Cleveland.
Common Duct Exploration and Acute Cholecystitis. FRANK GLENN, M.D., F.A.C.S., New York.
Primary Closure of the Common Duct. WILLIAM F. RIENHOFF, JR., M.D., F.A.C.S., Baltimore.
Extrahepatic Biliary Surgery in Children. ROBERT J. IZANT, JR., M.D., Columbus, Ohio.

Thursday, 8:30—11:30 a.m.

THE SPHINCTER OF ODDI

HENRY K. RANSOM, M.D., F.A.C.S., Ann Arbor, *Moderator.*

Anatomy of the Sphincter. NORMAN W. THIESSEN, M.D., F.A.C.S., Cleveland.
Physiology of the Sphincter. CHARLES B. PUESTOW, M.D., F.A.C.S., Chicago.
Indications for Sphincterotomy. ALAN THAL, M.D., Minneapolis.
Operative Cholangiography and the Sphincter. PHILIP F. PARTINGTON, M.D., F.A.C.S., Cleveland.
Technique of Sphincterotomy. RICHARD B. CATTELL, M.D., F.A.C.S., Boston.
Follow-up of Patients Having Had a Sphincterotomy. HENRY DOUBILET, M.D., F.A.C.S., New York.

Friday, 8:30—11:30 a.m.

THE PANCREAS

RICHARD L. VARCO, M.D., F.A.C.S., Minneapolis, *Moderator.*

The Natural History of Pancreatitis. JOHN M. HOWARD, M.D., F.A.C.S., Philadelphia.
Pancreatography. HENRY DOUBILET, M.D., F.A.C.S., New York.
Resection of the Pancreas for Chronic Pancreatitis. WILLIAM P. LONGMIRE, JR., M.D., F.A.C.S., Los Angeles.
Pancreatic Jejunostomy. MERLIN K. DUVAL, JR., M.D., Oklahoma City.
Pancreatic Cystogastrostomy. CHARLES B. PUESTOW, M.D., F.A.C.S., Chicago.
Pancreatic Tumors and Peptic Ulcer. EDWIN H. ELLISON, M.D., F.A.C.S., Milwaukee.
Pancreatectomy for Carcinoma of the Head of the Pancreas. JONATHAN E. RHOADS, M.D., F.A.C.S., Philadelphia.

COMPLEX, COMBINED, AND COMPLICATED INJURIES

OSCAR P. HAMPTON, JR., M.D., F.A.C.S., St. Louis, *Chairman.*

Tuesday, 8:30—11:30 a.m., Francis I Room, Pick-Congress Hotel

SKELETAL INJURIES OF THE EXTREMITIES COMPLICATED BY OTHER LIFE-ENDANGERING INJURIES

OSCAR P. HAMPTON, JR., M.D., F.A.C.S., St. Louis, *Moderator.*

Evaluation and Treatment of Head Injuries. LEONARD T. FURLOW, M.D., F.A.C.S., St. Louis.
Evaluation and Treatment of Chest Injuries. THOMAS H. BURFORD, M.D., F.A.C.S., St. Louis.
Diagnosis and Treatment of Intra-abdominal Injuries in the Presence of Fractures of the Spine and Pelvis. CARL E. LISCHER, M.D., F.A.C.S., St. Louis.

Management of Severe Extremity Injuries in the Presence of Life-Endangering Injuries of Head, Chest, or Abdomen. OSCAR P. HAMPTON, JR., M.D., F.A.C.S., St. Louis.

Wednesday, 8:30—11:30 a.m.

COMPLEX AND COMPLICATED FRACTURES AND FRACTURE-DISLOCATIONS OF THE LOWER EXTREMITY

EDWIN FRENCH CAVE, M.D., F.A.C.S., Boston, *Moderator.*
Fractures and Fracture-Dislocations of the Hip. GEORGE O. EATON, M.D., Baltimore.
Fractures and Fracture-Dislocations of the Knee. EARL P. HOLT, JR., M.D., F.A.C.S., St. Louis.
Fractures and Fracture-Dislocations of the Ankle. OTTO E. AUFRANC, M.D., F.A.C.S., Boston.
Fractures and Fracture-Dislocations of the Foot. FLOYD H. JERGESEN, M.D., F.A.C.S., San Francisco.

Thursday, 8:30—11:30 a.m.

COMPLEX AND COMPLICATED LONG BONE FRACTURES

HARRISON L. MCLAUGHLIN, M.D., F.A.C.S., New York, *Moderator.*
Operative Treatment. CHARLES S. NEER II, M.D., F.A.C.S., New York.
Nonoperative Treatment. HERBERT F. MOSELEY, M.D., F.A.C.S., Montreal.
Management of Multiple Fractures. BARBARA B. STIMSON, M.D., F.A.C.S., Poughkeepsie.
Reconstruction of Malunion and Nonunion. ALEXANDER P. AITKEN, M.D., F.A.C.S., Brookline.

Friday, 8:30—11:30 a.m.

COMPLICATED WOUNDS AND INJURIES OF SOFT AND SKELETAL TISSUES

PRESTON A. WADE, M.D., F.A.C.S., New York, *Moderator.*
Management of Deep Wounds of Extremities (Except Hand). F. H. JERGESEN, M.D., F.A.C.S., San Francisco.
Timing in the Repair of Complex Wounds of the Hand. VINTON E. SILER, M.D., F.A.C.S., Cincinnati.
Peripheral Nerve Injuries. FRANK H. MAYFIELD, M.D., F.A.C.S., Cincinnati.
Management of Patients with 30 to 50 Per Cent Burns. CURTIS P. ARTZ, M.D. F.A.C.S., Jackson, Mississippi.

INJURIES AND OTHER DISABILITIES OF THE HIP

HAROLD A. SOFIELD, M.D., F.A.C.S., Chicago, *Chairman.*

Tuesday, 8:30—11:30 a.m., Boulevard Room, The Conrad Hilton

Nailing of Fresh Fractures of the Neck of the Femur. MATHER CLEVELAND, M.D., F.A.C.S., New York.
Treatment of Intertrochanteric Fractures of the Hip. RALPH SOTO-HALL, M.D., F.A.C.S., San Francisco.
Osteotomies and Fusions for Ununited Hip Fractures. JAMES A. DICKSON, M.D., F.A.C.S., Cleveland.
Prostheses and Cups for Ununited Hip Fractures. JOSEPH S. BARR, M.D., F.A.C.S., Boston.
Treatment of the Smashed Acetabulum. PHILIP D. WILSON, JR., M.D., F.A.C.S., New York.

Wednesday, 8:30—11:30 a.m.

Congenital Deformities of the Hip. EDWARD A. MILLAR, M.D., Chicago.
Common Diseases of the Hip in Children. H. RELTON MCCARROLL, M.D., St. Louis.
Arthritic Hips in Children. ALFRED R. SHANDS, JR., M.D., Wilmington.
Death of the Head of the Femur from Use of Radium. ROBERT J. HASTERLIK, M.D., F.A.C.P., Chicago.
Bone Tumors of the Hip. C. HOWARD HATCHER, M.D., Chicago.

Thursday, 8:30—11:30 a.m.

Aseptic Necrosis of the Head of the Femur. SAM W. BANKS, M.D., F.A.C.S., Chicago.
Pathology and Differential Diagnosis of Arthritis of the Hip. JAMES F. KURTZ, M.D., Chicago.
Medical Treatment of Arthritis of the Hip. MAX M. MONTGOMERY, M.D., F.A.C.P., Chicago.
Treatment of Arthritis of the Hip by Cups and Prostheses. OTTO E. AUFRANC, M.D., F.A.C.S., Boston.
Treatment of Arthritis of the Hip by Osteotomies and Fusions. WALTER P. BLOUNT, M.D., F.A.C.S., Milwaukee.

Friday, 8:30—11:30 a.m.

Old and New Surgical Approaches to the Hip Joint. JAMES K. STACK, M.D., F.A.C.S., Chicago.
Dislocations of the Hip and Their Complications. JACK WICKSTROM, M.D., F.A.C.S., New Orleans.
Trochanteric Bursitis, Snapping Hips, Sprains of Hip. CHARLES ROMBOLD, M.D., F.A.C.S., Wichita, Kansas.
Long Term Follow-Up of Nailed Fractures of the Neck of the Femur. JAMES P. AHSTROM, JR., M.D., Chicago.
Summary: Choice of Treatment. HAROLD A. SOFIELD, M.D., F.A.C.S., Chicago.

SURGICAL ASPECTS OF PULMONARY DISEASE

EDWARD M. KENT, M.D., F.A.C.S., Pittsburgh, *Chairman.*

Monday, 1:30—4:30 p.m., Upper Tower, The Conrad Hilton

SYMPOSIUM ON PULMONARY PHYSIOLOGY

The Physiology of the Normal Chest. JOHN H. GIBBON, JR., M.D., F.A.C.S., Philadelphia.
Physiology of the Open Chest. FRANK F. ALLBRITTEN, JR., M.D., F.A.C.S., Kansas City, Kansas.
The Medical and Surgical Aspects of Cor Pulmonale. WILLIAM E. ADAMS, M.D., F.A.C.S., Chicago.
The Physiological Selection of Patients for Pulmonary Resection. PAUL NEMIR, JR., M.D., F.A.C.S., Philadelphia.
Panel: Physiology of the Thorax.
Moderator: JOHN H. GIBBON, JR., M.D., F.A.C.S., Philadelphia.
Collaborators: WILLIAM E. ADAMS, M.D., F.A.C.S., Chicago; FRANK F. ALLBRITTEN, JR., M.D., F.A.C.S., Kansas City, Kansas; PAUL NEMIR, JR., M.D., F.A.C.S., Philadelphia.

Tuesday, 1:30—4:30 p.m.

SYMPOSIUM ON PRESENT CONCEPTS OF THE SURGICAL TREATMENT OF FAR-ADVANCED PULMONARY TUBERCULOSIS (THE SO-CALLED SALVAGE CASE)

Preoperative and Postoperative Management by Chemotherapeutic Drugs. MARJORIE M. PYLE, M.D., Chicago.
Surgical Collapse Procedures in the Management of the Patient Having Far Advanced Pulmonary Tuberculosis. WILLIAM M. LEES, M.D., F.A.C.S., Chicago.
Pulmonary Resection in the Surgical Management of Far Advanced Pulmonary Tuberculosis. HIRAM T. LANGSTON, M.D., F.A.C.S., Chicago.
The Management of Tuberculous Empyema and Bronchopleural Fistula Following Pulmonary Resection. LYMAN A. BREWER III, M.D., F.A.C.S., Los Angeles.
Panel: The Surgical Management of the Patient with Pulmonary Tuberculosis.
Moderator: HIRAM T. LANGSTON, M.D., F.A.C.S., Chicago.
Collaborators: LYMAN A. BREWER III, M.D., F.A.C.S., Los Angeles; WILLIAM M. LEES, M.D., F.A.C.S., Chicago; MARJORIE M. PYLE. M.D., Chicago.

Wednesday, 1:30—4:30 p.m.

SYMPOSIUM ON COMMON PROBLEMS IN THORACIC SURGERY

Esophagitis. RICHARD H. SWEET, M.D., F.A.C.S., Boston.
The Management of Empyema. WILLIAM M. TUTTLE, M.D., F.A.C.S., Detroit.
The Surgical Management of Suppurative Diseases of the Lung. WATTS R. WEBB, M.D., F.A.C.S., Jackson.
The Management of Cystic Diseases of the Lung. DONALD L. PAULSON, M.D., F.A.C.S., Dallas.
Panel: Common Problems in Thoracic Surgery.
Moderator: RICHARD H. SWEET, M.D., F.A.C.S., Boston.
Collaborators: DONALD L. PAULSON, M.D., F.A.C.S., Dallas; WILLIAM M. TUTTLE, M.D., F.A.C.S., Detroit; WATTS R. WEBB, M.D., F.A.C.S., Jackson, Mississippi.

Thursday, 1:30—4:30 p.m.

SYMPOSIUM ON INTRATHORACIC NEOPLASMS

Bronchogenic Carcinoma. BRIAN BLADES, M.D., F.A.C.S., Washington, D. C.
Adenoma of the Bronchus. CHARLES K. KIRBY, M.D., F.A.C.S., Philadelphia.
Mediastinal Tumors. FREDERICK G. KERGIN, M.D., F.R.C.C., Toronto.
Radiation Therapy in Tumors of the Thorax. EUGENE R. KUTZ, M.D., Pittsburgh.
Chemotherapy in the Management of Intrathoracic Neoplasms. A. R. CURRERI, M.D., F.A.C.S., Madison.
Panel: Intrathoracic Neoplasms.
Moderator: BRIAN BLADES, M.D., F.A.C.S., Washington, D. C.
Collaborators: ANTHONY R. CURRERI, M.D., F.A.C.S., Madison, Wisconsin; FREDERICK G. KERGIN, M.D., Toronto; CHARLES K. KIRBY, M.D., F.A.C.S., Philadelphia; EUGENE R. KUTZ, M.D., Pittsburgh.

PROBLEMS IN PEDIATRIC SURGERY

WILLIS J. POTTS, M.D., F.A.C.S., Chicago, *Chairman.*

Tuesday, 8:30—11:30 a.m., Beverly Room, The Conrad Hilton

GENERAL CONSIDERATIONS

Preparation of Child for Surgery—Physical and Psychological. HUGH B. LYNN, M.D., F.A.C.S., Louisville.

Anesthesia and Temperature Control. GLENN R. WEYGANDT, M.D., Peoria.
Fluid Balance During Infancy. THOMAS G. BAFFES, M.D., F.A.C.S., Chicago.
Postoperative Care Is Demanding. WILLIAM B. KIESEWETTER, M.D., F.A.C.S., Pittsburgh.

Wednesday, 8:30—11:30 a.m.

COMMON PROBLEMS IN PEDIATRIC SURGERY

The Management of Hemangiomas. WILLIAM L. RIKER, M.D., F.A.C.S., Chicago.
Inguinal and Umbilical Hernia. H. WILLIAM CLATWORTHY, JR., M.D., F.A.C.S., Columbus, Ohio.
What About Undescended Testicles? ROBERT E. GROSS, M.D., F.A.C.S., Boston.
Pyloric Stenosis. STEPHEN L. GANS, M.D., F.A.C.S., Beverly Hills, California.
Intussusception—To Operate or Not to Operate. LAWRENCE K. PICKETT, M.D., F.A.C.S., Syracuse.

Thursday, 8:30—11:30 a.m.

ANOMALIES OF THE GASTROINTESTINAL TRACT

Roentgenography as an Aid in Diagnosis. HARVEY WHITE, M.D., Chicago.
Atresia of the Bowel. TAGUE C. CHISHOLM, M.D., F.A.C.S., Minneapolis.
Imperforate Anus and Its Complications. ALEXANDER H. BILL, JR., M.D., F.A.C.S., Seattle.
Hirschsprung's Disease in Infancy. ORVAR SWENSON, M.D., F.A.C.S., Boston.

Friday, 8:30—11:30 a.m.

RESPIRATORY PROBLEMS

Respiratory Infections in Surgical Wards. ROBERT J. IZANT, JR., M.D., Columbus, Ohio.
Respiratory Emergencies in the Newborn. IRVING A. MEEKER, JR., M.D., Los Angeles.
Diaphragmatic Hernia in the Newborn. C. EVERETT KOOP, M.D., F.A.C.S., Philadelphia.
Postpneumonic Lung Cysts. ARTHUR DEBOER, M.D., F.A.C.S., Chicago.
Pectus Excavatum. KENNETH J. WELCH, M.D., F.A.C.S., Brookline.

CARDIOVASCULAR SURGERY

ORMAND C. JULIAN, M.D., F.A.C.S., Chicago, *Chairman.*

Tuesday, 8:30—11:30 a.m., Florentine Room, Pick-Congress Hotel

SURGERY OF ACQUIRED HEART DISEASE

ORMAND C. JULIAN, M.D., F.A.C.S., Chicago, *Presiding.*
Selection of Patients and Long Term Results in Mitral Stenosis. JULIAN JOHNSON, M.D., F.A.C.S., Philadelphia.
Surgery of Mitral Regurgitation. EARLE B. KAY, M.D., F.A.C.S., Cleveland.
Surgery of Aortic Stenosis (Hypothermia). HENRY SWAN, M.D., F.A.C.S., Denver.
Aortic Valve Surgery Using Cardiac Bypass. C. WALTON LILLEHEI, M.D., F.A.C.S., Minneapolis.
Management of Cardiac Arrest. FRANK C. SPENCER, M.D., Baltimore.
Panel: Open Surgery for Acquired Valve Disease.
Moderator: ALFRED BLALOCK, M.D., F.A.C.S., Baltimore.
Collaborators: DONALD B. EFFLER, M.D., F.A.C.S., Cleveland; J. GORDON SCANNELL, M.D., F.A.C.S., Boston; CHARLES A. HUFNAGEL, M.D., F.A.C.S., Washington, D. C., ORMAND C. JULIAN, M.D., F.A.C.S., Chicago.

Wednesday, 8:30—11:30 a.m.

ARTERIAL RECONSTRUCTION

HARRIS B. SHUMACKER, JR., M.D., F.A.C.S., Indianapolis, *Presiding.*
Indications and Limitations of Reconstruction in Peripheral Arteriosclerosis.
D. EMERICK SZILAGYI, M.D., F.A.C.S., Detroit.
Prostheses in Peripheral Arterial Surgery. WILLIAM S. DYE, M.D., F.A.C.S., Chicago.
Aortico-iliac Occlusions. RICHARD WARREN, M.D., F.A.C.S., Boston.
Thoracic Aorta Surgery. MICHAEL E. DEBAKEY, M.D., F.A.C.S., Houston.
Abdominal Aneurysms. RALPH A. DETERLING, JR., M.D., F.A.C.S., New York.
Panel: Behavior of Graft Materials.
Moderator: RALPH A. DETERLING, JR., M.D., F.A.C.S., New York.
Collaborators: OSCAR CREECH, JR., M.D., F.A.C.S., New Orleans; ALFRED W. HUMPHRIES, M.D., F.A.C.S., Cleveland; JERE W. LORD, JR., M.D., F.A.C.S., New York; W. STERLING EDWARDS III, M.D., F.A.C.S., Chicago.

Thursday, 8:30—11:30 a.m.

CONGENITAL HEART DISEASE

ORMAND C. JULIAN, M.D., F.A.C.S., Chicago, *Presiding.*
Interauricular Septal Defects. F. JOHN LEWIS, M.D., F.A.C.S., Chicago.
Interventricular Septal Defects. FRANK GERBODE, M.D., F.A.C.S., San Francisco.
Tetralogy of Fallot. JOHN W. KIRKLIN, M.D., F.A.C.S., Rochester, Minnesota.
Surgical Anatomy of the Cardiac Conduction System. MAURICE LEV, M.D., Chicago.
Atrioventricular Canal. DENTON A. COOLEY, M.D., F.A.C.S., Houston.
Panel: Technical Aspects of Cardiac Bypass.
Moderator: C. WALTON LILLEHEI, M.D., F.A.C.S., Minneapolis.
Collaborators: HENRY T. BAHNSON, M.D., F.A.C.S., Baltimore; GEORGE H. A. CLOWES, JR., M.D., F.A.C.S., Cleveland; F. DEWEY DODRILL, M.D., F.A.C.S., Detroit.

Friday, 8:30—11:30 a.m.

PERIPHERAL VASCULAR PROBLEMS

CARL DAVIS, JR., M.D., F.A.C.S., Chicago, *Presiding.*
Surgery of Superior Vena Cava Obstruction. C. ROLLINS HANLON, M.D., F.A.C.S., St. Louis.
Acute Arterial Occlusion. ROBERT R. LINTON, M.D., F.A.C.S., Brookline, Massachusetts.
Surgery of Branches of the Aortic Arch. HUSHANG JAVID, M.D., F.A.C.S., Chicago.
Inflammatory Arterial Disease. GEZA DETAKATS, M.D., F.A.C.S., Chicago.
Arterial Trauma. J. C. LUKE, M.D., F.A.C.S., Montreal.
Panel: Coronary Artery Surgery.
Moderator: WILLIAM P. LONGMIRE, JR., M.D., F.A.C.S., Los Angeles.
Collaborators: ROBERT P. GLOVER, M.D., F.A.C.S., Philadelphia; JOHN H. GRINDLAY, M.D., F.A.C.S., Rochester, Minnesota; WILLIAM E. ADAMS, M.D., F.A.C.S., Chicago.

GYNECOLOGY AND OBSTETRICS

M. EDWARD DAVIS, M.D., F.A.C.S., Chicago, *Chairman.*

Monday, 8:30—11:30 a.m., Gold Room, Pick-Congress Hotel

WHAT CAN YOU DO FOR THE INFERTILE COUPLE?

What is New in Infertility? CHARLES M. MCLANE, M.D., New York.
Diagnostic Procedures for the Demonstration of Tubal Patency. HERBERT H. THOMAS, M.D., Birmingham.
Semen Quality and Sperm Survival in Cervical Mucus as Related to Fertility. SHELDON A. PAYNE, M.D., Los Angeles.
Prosaic Aspects of Infertility. ROBERT B. WILSON, M.D., F.A.C.S., Rochester, Minnesota.
Psychometric Testing in Sterility. ROBERT N. RUTHERFORD, M.D., Seattle.

Tuesday, 8:30—11:30 a.m.

INTELLIGENT HORMONAL THERAPY IN OBSTETRICS AND GYNECOLOGY

The Rationale of Endocrine Therapy. C. LEE BUXTON, M.D., New Haven.
Differential Diagnosis in Functional Gynecologic Disorders. GARDNER M. RILEY, M.S., PH.D., Ann Arbor.
Estrogens in Obstetrics and Gynecology. FRANCIS M. INGERSOLL, M.D., F.A.C.S., Boston.
Corticoids in Obstetrics and Gynecology. ROBERT B. GREENBLATT, M.D., Augusta, Georgia.
The Clinical Use of the New Progestational Steroids. EDWARD T. TYLER, M.D., Los Angeles.

Wednesday, 8:30—11:30 a.m.

THE HEMORRHAGIC COMPLICATIONS OF PREGNANCY

The Diagnosis of Ectopic Gestation. JAMES H. FERGUSON, M.D., F.A.C.S., Miami.
Abruptio Placentae. ISADORE DYER, M.D., F.A.C.S., New Orleans.
Fibrinogen-Fibrin Conversion Syndrome and Abruptio Placentae. C. PAUL HODGKINSON, M.D., F.A.C.S., Detroit.
Diagnostic and Therapeutic Studies on Choriocarcinoma and Related Trophoblastic Tumors. ROY HERTZ, M.D., Bethesda.
The Habitual Aborter. E. JURGEN PLOTZ, M.D., Chicago.

Thursday, 8:30—11:30 a.m.

THE MULTIDISCIPLINARY APPROACH TO MATERNITY CARE

The Obstetrician. ROBERT H. BARTER, M.D., F.A.C.S., Washington, D. C.

The Nurse-Educator. ANN KIRCHNER, R.N., Chicago.
The Pediatrician. JOHN L. REICHERT, M.D., Chicago.
The Nutritionist. Speaker to be announced.
The Social Worker. MRS. MARY J. CLARK, Chicago.

Forum on Fundamental Surgical Problems

Monday, 8:30 a.m.–12:00 noon

HEART AND EXTRACORPOREAL CIRCULATION

Myocardial Metabolism During Prolonged Asystole and Cardiopulmonary Bypass. PHILLIP M. IKINS, DANIEL M. ENERSON, and C. BARBER MUELLER, Syracuse.

Studies in Divided Coronary Blood Flow; Left and Right Ventricular Dynamics in the Bypassed Right Heart. Robert S. LITWAK, WILLIAM H. MEYER, JR., RALPH J. SLONIM, MARVIN B. SLOTKIN, and CLEMENE OCA, Coral Gables, Florida.

Pathologic Changes After Cardiopulmonary Bypass. PETER KOTTMEIER, JACKSON STUCKEY, JANIS ADAMSONS, MELVIN NEWMAN, and CLARENCE DENNIS, Brooklyn.

Studies in the Physiology of Oxygen Consumption During Cardiopulmonary Bypass. ROY R. VETTO, LOREN C. WINTERSCHEID, and K. ALVIN MERENDINO, Seattle.

A Method for the Detection of Microbubbles Resulting from the Passage of Blood Through Heart-Lung Machines. RONALD TEPPER, SOL GELMAN, ALBERT B. LOWENFELS, and JERE W. LORD, JR., New York.

A Study of Changes in Peripheral Flow and Resistance as Associated with Total Body Perfusion. JAY L. ANKENEY, PETER H. VILES, and JACK R. LEONARDS, Cleveland.

Studies of Blood Flow and Metabolism in Different Organs During Extracorporeal Circulation. KEITH REEMTSMA, M. MARTIN HALLEY, WILLIAM M. LETSON, and OSCAR CREECH, JR., New Orleans.

Treatment of Cardiac Arrest with Extracorporeal Circulation; Description of a Small Capacity, Instantly Available Pump-Oxygenator. M. MARTIN HALLEY, DENNIS M. L. ROSENBERG, EDWARD HYMAN, KEITH REEMTSMA, and OSCAR CREECH, JR., New Orleans.

An Inexpensive, Easy Method of Continuously Measuring Flow Rates in Extracorporeal Circulation. D. P. HALL, E. L. BRACKNEY, and R. G. ELLISON, Augusta, Georgia.

Tissue Oxygen "Tension" at Various Flow Rates of Extracorporeal Circulation. SEYMOUR I. SCHWARTZ, JAMES A. DEWEESE, FAUSTINO N. NIGUADULA, PAUL V. GABEL, and EARLE B. MAHONEY, Rochester, New York.

The Effects of Intra-arterial Air Injection on the EEG, EKG, Arterial, and Venous Blood Pressure. S. FRANK REDO, New York.

Experimental and Clinical Use of the Autogenous Lungs in Open Cardiac Surgery. GUMERSINDO BLANCO, CLEMENTE OCA, SALVADOR LAGUNA, LUIS E. NUÑEZ, JACK SCHAEFER, E. REY-BALTAR, and CHARLES P. BAILEY, Philadelphia.

Monday, 8:30 a.m.–12:00 noon

TUMORS

The Growth of Human Tumor Cells in Tissue Culture. G. E. MOORE and D. T. MOUNT, Buffalo.

The Viability of Circulating Cancer Cells in Experimental Cancer. OLGA JONASSON, Chicago.

A New Technique for the Detection of Tumor Cells in the Blood Stream and Its Application to the Study of the Dissemination of Cancer. JOHN F. POTTER and RICHARD A. MALMGREN, Bethesda.

The Effect of an Immune Serum and Cytotoxic Drugs on a Transplantable Tumor. FREDERICK W. PRESTON GEORGE C. HENEGAR, E. J. JACKSON, and ROBERT SCHREK, Chicago.

The Carcinogenic Effect of Nitrogen Mustard. GERALD O. MCDONALD and M. M. GOODWIN, Chicago.

Exploratory Study of Vascular Occlusion and Perfusion Techniques for the Localization of Action of Cytotoxic Agents. W. M. PARKINS, ROBERT G. RAVDIN, and PETER F. COGGINS, III, Philadelphia.

The Response of Cancer Cells in the Circulating Blood to Chemotherapy and Surgical Stress. STUART S. ROBERTS, ALVIN L. WATNE, RUTH G. MCGRATH, ELIZABETH R. MCGREW, and WARREN H. COLE, Chicago.

Control of Free Tumor Cell Growth by Topical Chemotherapeutic Agents. COLIN G. THOMAS, JR., PAUL M. WEEKS, and BOBBY C. BROWN, Chapel Hill, North Carolina.

An Assay Technic for Testing Cancer Therapeutic Agents for Clinical Use. JOSEPH A. DIPAOLO and GEORGE E. MOORE, Buffalo.

Limitations and Adverse Effects of Chemotherapy. TATSUHEI KONDO and GEORGE E. MOORE, Buffalo.

An In Vitro Test for Estrogen Dependence of Breast Cancer. FALLS B. HERSHEY, St. Louis.

Etiology of Inflammatory Reactions in Breast Carcinoma. JAMES T. GRACE, JR., and THOMAS L. DAO, Buffalo.

Monday, 8:30 a.m.–12:00 noon

GASTROINTESTINAL TRACT

Spontaneous Regeneration and Tubulation of an Open Strip of Esophageal Wall to Form a Functional Esophagus. FRANK C. MARCHETTA, ROY T. JOHNSON, and HENRY C. RIEGLER, Buffalo.

Immediate Reconstruction of the Cervical Esophagus by a Revascularized Isolated Jejunal Segment. BERNARD SEIDENBERG and ELLIOTT S. HURWITT, New York.

The Experimental Production of Cardiospasm in Dogs. DAVID M. LONG, CHARLES NICE, ALAN P. THAL, and RAYMOND C. TRUEX, Minneapolis.

The Cause of Fatalities in Bilateral Vagotomies. R. D. SLOAN, W. R. WEBB, and S. S. LEE, Jackson, Mississippi.

Experimental Production of Atrophic Gastritis. E. H. STORER, F. C. NANCE, D. T. DODD, J. CAMPBELL, and R. A. PARRISH, Memphis.

Modification of Gastrin Mechanism by Antroneurolysis. R. V. DEVITO, T. W. JONES, A. J. MARTINIS, L. M. NYHUS, and HENRY N. HARKINS, Seattle.

Studies on the Role of Nervous Mechanisms in Antral Function. DONALD E. WOHLRABE and WILLIAM D. KELLY, Minneapolis.

Gastric Secretion in the Fasting State and After Antral Stimulation in Patients with Cirrhosis and with Portacaval Shunts. JAMES S. CLARKE, ROBERT COSTARELLA, and SYLVESTER WARD, Los Angeles.

The Effect of Cortisone and Diet on the Acid Secretion of the Heidenhain Pouch. R. E. WIEDERANDERS, K. L. CLASSEN, and W. G. GOBBEL, JR., Nashville.

The Secretory Response of the Denervated Gastric Pouch to Prolonged Massive Cortisone Administration. LAWRENCE S. MCGEE, JR., JOHN BLACKBURN, EDWARD M. LANCE, and H. WILLIAM SCOTT, JR., Nashville.

Full Thickness Gastric Mucosal Excision in Cats with Prolonged Survival; Resistance to Histamine-Induced Ulceration. F. R. C. JOHNSTONE, Vancouver.

Total Excision of the Acid-Secreting Mucosa in the Dog. H. T. G. WILLIAMS, W. PISESKY, and WALTER C. MACKENZIE, Edmonton.

Monday, 1:30–5:00 p.m.

LIVER AND BILIARY TRACT

Cholesterol Synthesis in Human Liver. C. DAVIS, JR., G. E. COX, C. BRUCE TAYLOR, and S. L. CROSS, Chicago.

Studies on Hepatic Physiology in the Isolated, Perfused Calf Liver. A. J. MARTINIS, P. D. GOLDSWORTHY, T. W. JONES, L. M. NYHUS, R. V. DEVITO, W. VOLWILER, and H. N. HARKINS, Seattle.

Use of the Isolated Liver for Metabolic Studies. JOSEPH E. SOKAL, Rochester, New York.

Effect of Severe Injury on Liver Regeneration. STANLEY M. LEVENSON, LEO V. CROWLEY, JAMES F. OATES, and ANDRE D. GLINOS, Washington, D. C.

Studies of Liver Function Following Partial Biliary Obstruction in the Dog. F. G. MURPHY, S. C. SKORYNA, and D. R. WEBSTER, Montreal.

Effects of Gradual Complete Occlusion of the Hepatic Veins. SAMUEL KLING and PETER B. ALLEN, Edmonton.

How Reliable Are Liver Function Tests? A Reappraisal in Dogs. JAMES SPELL and JAMES D. HARDY, Jackson, Mississippi.

The Differentiation of Medical from Surgical Jaundice by Means of Serum Transaminase and Iron Determinations. FRANZ GOLDSTEIN, DAVID SELIGSON, and PAUL NEMIR, JR. Philadelphia.

The Influence of Eck Fistulas upon Diuresis and Antidiuresis in the Dog. ARTHUR J. DONOVAN and CHARLES G. CHILD, III, Boston.

A Comparison of Galactose Clearance by the Liver Following Portacaval Transposition or Eck Fistula. JOHN Q. OWSLEY, JR., JOHN M. GOIN, JOHN C. CLARKE, HAROLD A. HARPER, and H. J. MCCORKLE, San Francisco.

Effect of Dietary Choline on Biliary Phospholipids Excretion. FUMIO NAKAYAMA, and CHARLES G. JOHNSTON, Detroit.

The Role of Stasis in the Formation of Gallbladder Stones. KAMIL IMAMOGLU, JOHN F. PERRY, JR., HARLAN D. ROOT, NORMAN W. CRISP, and CONRAD B. JENSON, Minneapolis.

Monday, 1:30–5:00 p.m.

TUMORS (Continued); TISSUE TRANSPLANTATION AND ENDOCRINES

Interaction Between Hamster Lymph Nodes and Human Cancers. LESTER P. EIDELHOCH and W. BRADFORD PATTERSON, Boston.

Melanoma Inhibition in Hamsters and Mice by Ortho, Meta and Para Phenylenediamine. VERNON RILEY and JOSEPH G. FORTNER, New York.

The Development of Thyroid Cancer and Other Abnormalities in Syrian Hamsters Maintained on an Iodine Deficient Diet. JOSEPH G. FORTNER, PHYLLIS GEORGE, and STEPHEN S. STERNBERG, New York.

The Action of 3,5,3, L-Triiodothyronine and Nitrogen Mustard on the "Take" of the Walker 256 Rat Tumor. LOREN J. HUMPHREY and FREDERIC A. DE PEYSTER, Chicago.

Ablation of Adrenal Estrogens in the Treatment of Far Advanced Mammary Cancer. GEORGE E. BLOCK, Ann Arbor, Michigan.

Studies in Endocrine Tissue Homotransplantation in the Dog Utilizing Millipore Filters—I, Survival of Grafts: Morphology and Fibroplasia. ROGER HALLIN, HENRY SWAN, BRIAN GORDON, and ROBERT TREASURE, Denver.

Studies on Tissue Homotransplantation in Dogs Using a New Type Diffusion Chamber. H. LEROY BROCKMAN, Houston.

Endocrine Tissue Homotransplantation in the Rat and Dog Using the Millipore Diffusion Chamber Technique. JOHN R. BROOKS, JULIO PRIARIO, and ALBERT DE SCOVILLE, Boston.

Studies on the Mechanism of Action of Adrenal Steroids Using Isolated Cell Systems. ALLAN D. BASS, and JAMES A. SETLIFF, Nashville.

Relationship Between Steroid Output in Adrenal Vein Blood and Steroid Formation of Adrenal Incubates of Hypertensive Patients. DAVID Y. COOPER, JOSEPH C. TOUCHSTONE, WILLIAM S. BLAKEMORE, and OTTO ROSENTHAL, Philadelphia.

Aldosterone Secretion Following Surgery; Correlation with the Urinary Na/K Ratio. LOUIS SULYA, JAMES SPELL, JEWELL SLOCUM, and JAMES D. HARDY, Jackson, Mississippi.

The Secretion of Epinephrine, Norepinephrine, and Corticosteroid in the Adrenal Venous Blood of the Human. DAVID M. HUME and C. COOPER BELL, JR., Richmond, Virginia.

Monday, 1:30–5:00 p.m.

ORTHOPEDIC SURGERY

The Effect of Certain Sex Hormones upon the Reparative Process in Fractures Following Motor Denervation in Rats. W. S. SMITH, R. F. SLAGER, and C. R. COLEMAN, Columbus, Ohio.

A Study of the Growth and Nutrition of Surgically Created Osteochondral Loose Bodies in Adult and Young Rabbits. ROBERT W. BAILEY and ROBERT E. SELLE, Los Angeles.

Metabolic Changes in Elderly Women with Fractures of the Hip. FRANCIS D. MOORE, A. W. R. WILLIAMSON, WILLIAM F. WALKER, and HENRY BANKS, Boston.

Fat Embolism; Changes in the Serum Lipase Levels of Patients After Fresh Fractures or Orthopedic Operations. LEONARD F. PELTIER and SING-PING LAI, Kansas City, Kansas.

Therapy of Traumatic Fat Embolism with Intravenous Fluids and Heparin. C. A. COBB, JR., V. S. LEQUIRE, M. E. GRAY, and J. W. HILLMAN, Nashville.

Experimental Studies on the Stability of Internal Fixation of Femoral Neck Fractures in Autopsy Bone. J. PAUL HARVEY, New York, CARL HIRSCH, Uppsala, Sweden, and PHILIP D. WILSON, New York.

Polyurethane Polymer; Its Use in Fractured and Diseased Bones. MICHAEL P. MANDARINO, and JOSEPH E. SALVATORE, Philadelphia.

Freeze-Dried Bone Homografts. M. K. MYINT, W. T. FITTS, JR., B. ROBERTS, J. JENNY, H. B. LEHR, and L. ANDERSON, Philadelphia.

Internal Fixative Device for Anterior Fusion of the Lumbar Spine. A. W. HUMPHRIES, Cleveland.

Experimental Study of Pyogenic Arthritis Due to Penicillin-Resistant Staphylococcus in Rabbits Treated with Intra-articular Broad Spectrum Antibiotics. CHARLES J. FRANKEL, DAVID K. WEBSTER, and A. BRANT LIPSCOMB, Charlottesville, Virginia.

The Effect of Environmental Influences on Acetabular Development. C. R. COLEMAN, R. SLAGER, and W. S. SMITH, Columbus, Ohio.

Bone and Joint Changes Following Burns. E. BURKE EVANS and J. R. SMITH, Galveston.

Tuesday, 8:30 a.m.–12:00 noon.

PLASTIC SURGERY

The Behavior of Skin Grafts Exchanged Between Parents and Offspring. LYNDON A. PEER and JOHN C. WALKER, JR., Newark, New Jersey.

The Altered Response to Skin Homografts and to Delayed Allergens in Hodgkin's Disease. W. D. KELLY, R. A. GOOD, and RICHARD L. VARCO, Minneapolis.

Studies of Protein Migration Between Host and Homograft. F. W. BARNES, H. G. KEMP, and MILTON T. EDGERTON, JR., Baltimore.

Studies on Mammalian Homografts; Tolerance Induced with a Pooled Antigen. FRANKLIN L. ASHLEY, HAROLD STEIN, AMOS N. SCHWARTZ, CHARLES CLIFFORD, SISTER GERTRUDE JOSEPH, ROBERT SLOAN, and WILLIAM P. LONGMIRE, JR., Los Angeles.

Acquired Tolerance for Homotransplantation of Normal Tissues and Organs. CARLOS MARTINEZ, JUNE M. SMITH, J. BRADLEY AUST, and ROBERT A. GOOD, Minneapolis.

Skin Homograft Rejection in Adrenalectomized Individuals Maintained on Meticorten. GEORGE F. CRIKELAIR and CADVAN O. GRIFFITHS, New York.

Cryobiology. STANLEY W. JACOB, OWEN E. OWEN, SAMUEL C. COLLINS, and J. ENGLEBERT DUNPHY, Boston.

Bacteriological Studies of the Burn Wound in Relation to Therapy and Skin Grafting Procedures. GILBERT G. EADE, S. R. LEWIS, and TRUMAN G. BLOCKER, JR., Galveston.

Effect of Total Body Irradiation on Biochemical Sequences in Granulation Tissue. DALE B. FLICKINGER, KEITH D. J. VOWLES, and J. ENGLEBERT DUNPHY, Boston.

Cannulation Studies of the Lymphatics of the Lower Extremity. J. R. SMITH, FRANK DUNTON, JACK PROTAS, R. N. COOLEY, S. R. LEWIS, and TRUMAN G. BLOCKER, JR., Galveston.

Healing of Tendons; Immobilization Versus Early Active Motion. JAMES H. HENDRIX, JR., and HEBER C. ETHRIDGE, Jackson, Mississippi.

Biological Reactions to Collagen Transplants. ERLE E. PEACOCK, JR., Chapel Hill, North Carolina.

Tuesday, 8:30 a.m.–12:00 noon.

PROBLEMS IN OPEN HEART SURGERY

An Autoclavable Stainless Steel Stationary Screen Oxygenator. JESSE E. ADAMS, EDWARD M. LANCE, BAILEY MOORE, and H. W. SCOTT, JR., Nashville.

The Bubble Oxygenator Versus the Screen Disc Oxygenator: Comparison of Function and of Effects. CHARLES C. FRIES, KARL E. KARLSON, STANLEY ARONSON, and CLARENCE DENNIS, Brooklyn.

A Method for Replacing the Aortic Arch in Dogs Maintaining Normal Blood Pressures with Two Pumps and Avoiding Prolonged Use of an Oxygenator. FRANK E. JOHNSON, JOSEPH A. DOWLEN, OREST FILIPOVICH, LEWIS E. HUGHES, and CLAUDE R. HITCHCOCK, Minneapolis.

Electrode Identification of the Conduction Bundle During Open Heart Surgery. JACKSON STUCKEY, BRIAN HOFFMAN, and PETER KOTTMEIER, Brooklyn.

Surgical Treatment of Aortic Insufficiency by Open Plastic Revision of Tricuspid Aortic Valve to a Bicuspid Valve. JOSEPH J. GARAMELLA, RUBEN OROPEZA, JAMES G. ANDERSON, and LYLE J. HAY, Minneapolis.

Gradual Closure of Interventricular Septal Defects. R. BENVENUTO and F. JOHN LEWIS, Chicago.

The Natural Course of Infants and Children with Ventricular Septal Defects. MILTON WEINBERG, ARCHER S. GORDON, EGBERT H. FELL, BENJAMIN M. GASUL, JOSHUA LYNFIELD, and LAWRENCE LUAN, Chicago.

Development of Interarterial Coronary Anastomoses by an Arteriovenous Fistula Between the Pulmonary Artery and the Left Atrium. STACEY B. DAY, VINCENT L. GOTT, JOHN A. JOHNSON, and OWEN H. WANGENSTEEN, Minneapolis.

Aortic Valve Replacement with a Subcoronary Ball Valve. W. STERLING EDWARDS and LLOYD SMITH, Birmingham.

General Hypothermia and Intragastric Cooling. MARSH HOLT, RICCARDO BENVENUTO, and F. JOHN LEWIS, Chicago.

Studies in Hypothermia and Its Use in Early Burn Therapy. H. HARLAN STONE and J. D. MARTIN, JR., Emory University, Georgia.

The Influence of Hypothermia on Cerebral Injury Resulting from Circulatory Occlusion. JACK M. ZIMMERMAN and FRANK C. SPENCER, Baltimore.

Tuesday, 8:30 a.m.–12:00 noon.

GASTROINTESTINAL TRACT (Continued)

Intraintestinal and Gastric *p*H Changes Following Billroth Gastrectomies. PETER SALMON, HARLAN D. ROOT, CONRAD B. JENSON, NORMAN W. CRISP, and KAMIL IMAMOGLU, Minneapolis.

Absolute Iron Absorption Following Subtotal Gastrectomy in the Dog. NOBUYUKI SHIOYA, SURYAKANT TALSANIA, RUSSELL C. BRIGGS, and SAMUEL R. POWERS, JR., Albany.

Experimental Production of Peptic Ulceration—a New Method. O. SILBERMAN, H. T. G. WILLIAMS, W. PISESKY, and R. C. HARRISON, Edmonton.

Genetic Factors in Duodenal Ulcer. JOSEPH A. BUCKWALTER and CAROLE A. BUCKWALTER, Iowa City.

A Method of Duodenal Stump Closure with Intact Omentum. ROBERT HARDIN, CHIEN SHENG SU, and JAMES S. BATTERSBY, Indianapolis.

The Role of Stomal Diameter in the Postgastrectomy Dumping Syndrome. WILLIAM SILEN, W. H. BROWN, and B. EISEMAN, Denver.

Studies in Postoperative Ileus; Intestinal Motility as Reflected in the Propulsion of Radiopaque Materials. JASPER L. MCPHAIL, SAM ROBINSON, JAMES D. HARDY, and J. HAROLD CONN, Jackson, Mississippi.

Localization of Upper Gastrointestinal Hemorrhage with the Fluorescein String Test. MITCHELL KARLAN and DONALD W. TRAPHAGEN, Columbus, Ohio.

A Smooth-Muscle Stimulating Substance Released from the Intestine Following Acute Arterial Occlusion. DONALD M. PERLMAN and JACK W. COLE, Cleveland.

The Relative Effects of Arterial Occlusion and Venous Occlusion on Intestinal Blood Flow. M. D. TURNER and WILLIAM A. NEELY, Jackson, Mississippi.

The Effect of Venous Obstruction on Acid Secretion and Portal Venous Oxygen Saturation. RICHARD M. PETERS and NATHAN A. WOMACK, Chapel Hill, North Carolina.

Urinary Excretion Products in Strangulation Obstruction. BENJAMIN B. JACKSON, Louisville.

Tuesday, 1:30–5:00 p.m.

PARENTERAL NUTRITION AND CIRCULATION

The Treatment of Pooled Human Plasma with Formaldehyde at 60 Degrees C. for Ten Hours; In Vitro Studies. ABDUL AL-SHAMMA, WILLIAM W. PFAFF, EDWARD A. STEMMER, and J. GARROTT ALLEN, Chicago.

The Treatment of Pooled Human Plasma with Formaldehyde at 60 Degrees C. for Ten Hours; Biologic Studies. WILLIAM W. PFAFF, EDWARD A. STEMMER, ABDUL AL-SHAMMA, and J. GARROTT ALLEN, Chicago.

The Effect of Whole Blood and Packed Red Cell Transfusions on Plasma Volume, Red Cell Volume, Extracellular Fluid Volume and Total Body Water in Patients with Anemia. JAMES D. MCMURREY and MICHAEL E. DE BAKEY, Houston.

Variations in the Technique of Platelet Preservation at −79 degrees C. WALTER F. BALLINGER, II and ARTHUR J. WEISS, Philadelphia.

The Antiheparin Properties of the Antihistamine and Tranquilizer Drugs. RUSSELL M. NELSON, JAMES O. MASON, and C. GORDON FRANK, Salt Lake City.

An Experimental Study of the Efficacy of Protamine Sulfate and Polybrene as Heparin Neutralizing Agents. WILLIAM J. MCCANN, RICARDO F. SEBASTIAN, JAMSHID KAVOUSSI, and JOHN L. MADDEN, New York.

The Use of Dextran Sulfate as an Anticoagulant for Open Heart Surgery. WILLIAM H. WADE and RAYMOND VICKERS, Columbia, Missouri.

Perfusion of Isolated Vascular Beds Using Blood Substitutes and Various Electrolyte Solutions. JAMES N. WINBLAD, ROBERT F. RYAN, and JEAN VERNHET, New Orleans.

The Effects of Heparin and Coumarin Derivatives on a Standardized Intravenous Thrombosis. ROGER D. WILLIAMS and DAN W. ELLIOTT, Columbus, Ohio.

The Hemolytic Effects of Fat Emulsion. HARRY H. LEVEEN, PRUDENCE GIORDANO, and GERALD FALK, Brooklyn.

Experimental Study of Intravenous Fat Emulsions. M. ATIK, JOSHUA C. WERNER, and ISIDORE COHN, JR., New Orleans.

A Method for the Measurement of Blood Flow in Isolated Segments of Small Bowel and Kidney in Dogs. WILLIAM A. NEELY and M. D. TURNER, Jackson, Mississippi.

Tuesday, 1:30–5:00 p.m.

MINERALS, METABOLISM, AND NUTRITION

Effectiveness of Salt Solutions in the Therapy of Burn Shock in Man. JERRY A. STIRMAN, BEN J. WILSON, Dallas.

Regulation of Aldosterone Output; Significance of Potassium Ion. WALTER H. MORAN, JR., J. C. ROSENBERG, and BERNARD ZIMMERMANN, Minneapolis.

Long Term Control of Ammonia Intoxication by Administration of Antibiotics. ARTHUR B. VOORHEES, JR., ARTHUR H. BLAKEMORE, ALAN C. MERCHANT, BALBINA JOHNSON, and HAROLD G. BARKER, New York.

The Site of Ammonia Production and Absorption in Eck Fistula Dogs. PAUL F. GRYSKA and ERNEST M. BARSAMIAN, Boston.

The Effect of Autonomic Nerve Section on Intestinal Absorption of Glucose. ROGER MESMER, HARRY W. HALE, JR., and MANUEL SCHREIBER, Buffalo.

The Metabolism of Ethanol in Man. DAVID SELIGSON, HRANT H. STONE, and PAUL NEMIR, JR., Philadelphia.

A Study of Differences in Fat Absorption Following Oral and Jejunal Administered I^{131} Labeled Fat. W. G. GOBBEL, JR., and H. H. SHOULDERS, JR., Nashville.

The Effect of Long Term Administration of Intravenous Fat on Liver Function and the Coagulation Mechanism. CURTIS P. ARTZ, WILLIAM FANT, and WARREN BELL, Jackson, Mississippi.

Performance in an Acute Cold Stress of Animals Having Differing Saturation of Body Fats. MICHAEL HUME, WILLIAM W. L. GLENN, and J. J. BARBORIAK, New Haven.

The Effects of Hydration on Epinephrine Induced Renal Shut Down in Dogs. CHARLES R. HATCHER, JR. JOHN A. GAGNON, and ROBERT W. CLARK, Washington, D. C.

Gastrodialysis with a Semipermeable Membrane Balloon; Application to Renal Failure and Other Metabolic Derangements. PAUL R. SCHLOERB, Kansas City, Kansas.

An Ion Exchange Resin Type Artificial Kidney. DAVID C. SCHECHTER, THOMAS F. NEALON, JR., and JOHN H. GIBBON, JR., Philadelphia.

Wednesday, 8:30 a.m.–12:00 noon.

CORONARY CIRCULATION AND COAGULATION

Evaluation of Cardiac Revascularization Procedures Using Myocardial Temperature Change During Temporary Coronary Artery Occlusion. JOHN B. BRAINARD, CLIFFORD M. PHIBBS, and LLOYD D. MACLEAN, Minneapolis.

Cardio-omentopexy and Implantation of Multiple Omental Loops for Revascularization of the Heart. FRANCES E. KNOCK, Chicago.

Experimental Study of the Anatomic and Physiologic Effects of Incisions into the Left Ventricle. W. DEAN WARREN, WILLIAM H. MULLER, JR., W. MARSHALL EAST, and OMER D. SOSA, Charlottesville, Virginia.

A Comparative Study of Diastolic and Systolic Phase Dye Injection in Human Coronary Arteriography. L. STEPHEN RICHARDS and ALAN P. THAL, Minneapolis.

Gross and Microscopic Sequelae in Experimentally Produced and Repaired Aortic Aneurysms. STEVEN G. ECONOMOU, C. BRUCE TAYLOR, and EDWARD J. BEATTIE, JR., Chicago.

Production of Lower Nephron Nephrosis in Dogs by Means of an Episode of Intravascular Clotting. R. M. HARDAWAY and D. G. MCKAY, Boston.

The Effect on the Kidneys of Cross Clamping the Aorta Distal to the Renal Arteries. J. G. NOBLE, ERIC M. NANSON, and HENRY ENSON, Saskatoon.

A Study of the Pressor Effects of Serotonin and Its Possible Role in Massive Thromboembolism. JOHN W. SULLENBERGER, WILLIAM T. WEAVER, JACOB I. FABRIKANT, and WILLIAM G. ANLYAN, Durham.

The Use of Plasmin for the Intraoperative Lysis of Clots Occurring During Experimental Arterial Surgery. J. LEONEL VILLAVICENCIO and RICHARD WARREN, Boston.

Hemodynamic Factors in Arterial Grafting; an Experimental Study of Anastomotic Types, Graft Size, and Graft Surface Characteristics. D. EMERICK SZILAGYI, JOHN G. WHITCOMB, PETER WAIBEL, and J. W. SCHENKER, Detroit.

A Basic Observation on the Ability of Newly Formed Capillaries to Develop into Collateral Arteries. WILLIAM H. SEWELL and DOUGLAS R. KOTH, Bethesda.

The Lysis of Artificially Induced Intravascular Clots in Man by Intravenous Infusion of Purified Streptokinase. ALAN J. JOHNSON, W. ROSS MCCARTY, and W. S. TILLETT, New York.

Wednesday, 8:30 a.m.–12:00 noon.

TRACHEA AND LUNG

An Improved Tracheal Prothesis. WILLIAM H. MONCRIEF, JR. and JOSEPH E. SALVATORE, Washington, D. C.

Extensive Segmental Resection of the Trachea with Primary Suture Anastomosis; an Experimental Study. MAX L. SOM and SAMUEL H. KLEIN, New York.

A Study on Respiratory Arrest Following the Administration of Neomycin. WILLIAM B. SHORT, JR., JACOB L. HARTLEY, and J. D. MARTIN, JR., Emory University, Georgia.

Respiratory Arrest Following Intraperitoneal Administration of Neomycin; an Experimental Study. MARVIN L. GLIEDMAN, ROBERT D. SELLERS, ROALD N. GRANT, NATHAN SPIER, BETTY VESTAL, and KARL E. KARLSON, Brooklyn.

Respiration Following Lung Denervation. L. P. FABER and E. J. BEATTIE, JR., Chicago.

A Study of Circulation in the Lung Following Pulmonary Artery Occlusion. RICHARD N. MOERSCH, DAVID E. DONALD, JOHN W. KIRKLIN, and JOHN H. GRINDLAY, Rochester, Minnesota.

The Effects of Reduction in Pulmonary Blood Flow upon the Pulmonary Circulation and Respiratory Gas Exchange. PAUL H. GERST, CHRISTEN RATTENBORG, and DUNCAN A. HOLADAY, New York.

Pulmonary Hemodynamics as Affected by Varying Levels of Respiratory Pressure. W. R. WEBB and J. R. SMITH, Jackson, Mississippi.

Changes in Pulmonary Vascular Lesions After Restoring Normal Pulmonary Artery Pressure. RICHARD H. BLANK, WILLIAM H. MULLER, JR., and J. FRANCIS DAMMANN, JR., Charlottesville, Virginia.

The Development of Chronic Pulmonary Hypertension. C. FREDERICK KITTLE, LUIS BIANCHINI, THEODORE HOSTETLER, and WILLIAM A. REED, Kansas City, Kansas.

Observations on the Effect of Norethandrolone in Favoring Anabolism in Patients Undergoing Pulmonary Resection for Tuberculosis. JOHN H. KENNEDY, HAROLD A. PETERS, and GEORGE S. SERIF, San Diego.

Pulmonary Edema Following Re-expansion of a Total Pneumothorax; a Clinical and Experimental Study. R. I. CARLSON, K. L. CLASSEN, W. G. GOBBEL, JR., D. E. SHERMAN, F. GOLLAN, and R. O. CHRISTENSEN, Nashville.

Wednesday, 8:30 a.m.–12:00 noon.

SHOCK

Survival in Acute Experimental Hemorrhage. VERNON MONTGOMERY, JEAN BLAVIER, DALTON JENKINS, and HENRY SWAN, DENVER.

Intestinal Factor in Irreversible Hemorrhagic Shock. LOUIS H. POWERS and PAUL R. SCHLOERB, Kansas City, Kansas.

The Role of the Small Intestine in Hemorrhagic Shock. J. M. MCRAE, W. R. WEBB, S. S. LEE, and J. C. GRIFFIN, JR., Jackson, Mississippi.

The Effect of Hemorrhagic Shock on Intestinal Blood Flow. ROBERT C. OVERTON, WALTER S. HENLY, JAMES D. MCMURREY, and MICHAEL E. DE BAKEY, Houston.

The Use of Intravenous Cortisone in Hemorrhagic Shock. JOHN E. CONNOLLY, DAVID L. BRUNS, and RAYMOND STOFER, San Francisco.

Metabolic Aspects of Hemorrhagic Shock. WILLIAM R. DRUCKER, MARTIN KAYE, RONALD KENDRICK, NANCY HOFFMAN, and BRYANT KINGSBURY, Cleveland.

The Effect of Methylene Blue and Ascorbic Acid in Hemorrhagic Shock. JOSEPH G. STRAWITZ, ROBERT L. TEMPLE, ALAN EHRHARDT, and HELEN HIFT, Madison, Wisconsin.

Hepatic Blood Flow and Hepatic Glucose Output in Hemorrhagic Shock. WILLIAM C. SHOEMAKER and WILLIAM F. WALKER, Boston.

Effect of Hydralazine on the Survival Rate of Dogs Subjected to Hemorrhagic Shock. WALTER ZINGG, MARK NICKERSON, and STEFAN A. CARTER, Winnipeg.

The Effect of Acute Addition Acidosis in Experimental Hemorrhagic Hypotension. LOUIS L. SMITH, A. WILLIAM R. WILLIAMSON, and FRANCIS D. MOORE, Boston.

Blood Flows to Various Tissues in Endotoxin Shock. J. B. AUST and JOHN JOHNSON, Minneapolis.

The Effect of Norepinephrine (Levophed) on Survival in Standard Oligemic Shock. JAMES C. GRIFFIN, JR., WATTS R. WEBB, JAMES D. HARDY, S. S. LEE, and JOHN M. MCRAE, JR., Jackson, Mississippi.

Wednesday, 1:30–5:00 p.m.

HEART AND CIRCULATORY PROBLEMS (Continued)

Comparison of Flat and Crimped Dacron Arterial Prosthesis Otherwise Identical. ORMAND C. JULIAN, H. H. SU, SAD EL-ISSA, ANDRE LIMA, and M. LOPEZ-BELIO, Chicago.

Experimental Production of Arteriosclerosis in the Dog. NORMAN W. CRISP, JR., HARLAN D. ROOT, CONRAD B. JENSON KAMIL IMAMOGLU, and EARL G. YONEHIRO, Minneapolis.

The Experimental Use of the Diaphragm as an Auxiliary Myocardium. ADRIAN KANTROWITZ, Brooklyn.

Cerebral Anoxia Resulting from Hyperventilation. W. G. MALETTE, Denver.

Hypotension and Myocardial Anoxia Associated with Selective Brain Cooling in the Dog. C. D. BUSTER and BYRON C. PEVEHOUSE, San Francisco.

Catheterization of the Left Heart Through the Interatrial Septum; a New Technic and Its Experimental Evaluation. JOHN ROSS, JR., Bethesda.

Study of the Effects of Controlled Cardiac Output in Thoracotomized Dogs. E. C. ELLIOT and J. C. CALLAGHAN, Edmonton.

The Effect of L-Norepinephrine on Cardiac Output and Hepatic Blood Flow in Experimental Acute Hemorrhagic Hypotension. B. A. PORTIN, M. B. LESLIE, and W. G. SCHENK, JR., Buffalo.

Experimental Evaluation of the Toxicity of Hypaque, Urokon, and Thorotrast Incident to Their Use as Aortographic Contrast Media. DUNCAN A. KILLEN, EDWARD M. LANCE, and GUY OWENS, Nashville.

Electrocardiographic Alterations Observed During Percutaneous Cerebral Angiography with Diodrast and Hypaque. JOSEPH A. EPSTEIN, IRWIN HOFFMAN, and BERNARD S. EPSTEIN, New Hyde Park, New York.

The Influence of Ligation of Intercostal Arteries on Paraplegia in Dogs. FRANK C. SPENCER and JACK M. ZIMMERMAN, Baltimore.

Further Studies of Renal and Adrenal Factors in the Hypertension of Experimental Coarctation. H. WILLIAM SCOTT, JR., LAWRENCE S. MCGEE, JR., ROBERT W. YOUNGBLOOD, DUNCAN A. KILLEN, A. PAGE HARRIS, and EDWARD M. LANCE, Nashville.

Wednesday, 1:30–5:00 p.m.

PANCREAS AND ASCITIC CONDITIONS

Studies in Pancreatic Exocrine Insufficiency. Joe W. Frazer, Jr., William G. Anlyan, and Joseph K. Isley, Durham.

Trypsin Inhibitor Levels in Experimental Pancreatitis. George W. Lampros and Victor Richards, San Francisco.

The Role of Trypsin and of Bile Salts in the Pathogenesis of Acute Pancreatitis. Dan W. Elliott, Roger D. Williams, and Robert M. Zollinger, Columbus, Ohio.

Cortisone in the Treatment of Experimental Acute Pancreatitis. William R. C. Stewart, Dan W. Elliott, and Robert M. Zollinger, Columbus, Ohio.

The Intracellular Enzymes Responsible for Pancreatic Necrosis. L. Corsan Reid, Robert E. Paulette, and J. William Hinton, New York.

The Relation of the Pancreas to Immune Body Formation. Robert E. Paulette, L. Corsan Reid, and J. William Hinton, New York.

The Effect of Pancreatectomy on the Incidence of Gastric Ulceration in the Shay Rat. René B. Menguy and Merlin K. DuVal, Jr., Oklahoma City.

Resorption of Experimental Ascites in the Dog by Ileoperitoneopexy. John T. Wilson and Charles G. Child, III, Boston.

The Production of Experimental Ascites and Experiences in Treatment with the Rectus Wick Operation. Sil H. Lee, Pittsburgh.

An Attempt to Determine the Source of Experimental Ascitic Fluid. Irving F. Enquist, Roy G. Aiello, Etsutaro Ikezono, and Bernard S. Levowitz, Brooklyn.

The Toxicity of Peritoneal Fluid Resulting from Strangulation at Different Levels of the Gastrointestinal Tract. Richard Doyle, Jackson, Mississippi.

A Study of Peritoneal Fluid After Strangulation Obstruction of the Ileum; the Apparent Role of Living Bacteria Rather Than a Free Endotoxin or Exotoxin as a Lethal Factor. William O. Barnett, M. Don Turner, and James B. Grogan, Jackson, Mississippi.

Thursday, 8:30 a.m.–12:00 noon.

UROLOGY

Calcium Binding Capacity of Urine in Patients with Calcium-Containing Renal Calculi. Arthur J. Butt and Reid H. Leonard, Pensacola, Florida.

A Study of the Renal Excretion of Calcium and Phosphorus in Patients with Renal Calculi. Sheridan W. Shirley, Richard E. Padrnos, Karlman Wasserman, and Edgar Burns, New Orleans.

Extracorporeal Kidney Perfusion. Gordon F. Cassie, Nathan P. Couch, and Joseph E. Murray, Boston.

The Renal Artery Homograft; an Experimental Study. Guy W. Leadbetter, Jr., Boston.

Detection of Renal Arterial Lesions Causing Hypertension in Dogs, Utilizing Radioisotope Renograms. Chester C. Winter, Los Angeles.

Separated Kidney Function Tests in Hypertensive Patients. Eugene F. Poutasse, Andrew Donnelly, and Harriet P. Dustan, Cleveland.

Creation of a Continent Urinary Bladder by Substitution of an Isolated Segment of Ileum. Charles L. Reynolds, Dallas.

Substitute Urinary Bladder Constructed from an Isolated Segment of Small Bowel. S. R. Weinberg, K. Waterhouse, F. Salerno, and Frank C. Hamm, Brooklyn.

Evaluation of a "Substitute Detrusor." J. J. Murphy, W. H. Rattner, and W. S. Blakemore, Philadelphia.

Assessment of the Role of the Kidney, Liver, and Colonic Mucosa in Hyperchloremic Acidosis; an Experimental Study. Ronald H. Hayward, Khalil G. Wakim, William H. ReMine, John H. Grindlay, and Jesse L. Bollman, Rochester, Minnesota.

Ureteral Substitution Using Vesical Mucosa Grafts in Nonreversed Seromuscular Ileal Segments; a Preliminary Report. Leonardo S. J. Martin, James H. Duxbury, and Wyland F. Leadbetter, Boston.

Transplantation of Bladder Mucosa to Intestinal Segments. Michel G. Gilbert, Robert J. Izant, Jr., and William Pace, III, Columbus, Ohio.

Thursday, 8:30 a.m.–12:00 noon.

GENERAL, ANESTHESIA AND LUNG (Continued)

A Quantitative Evaluation of the Permeability of Wet Surgical Drapes to Staphylococcus Aureus. Karl Karlson, William Riley, and Clarence Dennis, Brooklyn.

Gastric Pepsin Secretion in Patients with Cranial Injuries with Relation to the Development of Acute Peptic Ulcer. CLIFFORD M. PHIBBS and LLOYD D. MACLEAN, Minneapolis.

Experimental Studies on Acute Renal Tubular Degeneration Following Crush Injury. SAMUEL R. POWERS, JR., ANTONIO BOBA, NOBUYUKI SHIOYA, and ARTHUR A. STEIN, Albany.

Lactic Dehydrogenase Activity of Dog Plasma Following Renal Injury. MURRAY M. BETT, GLORIA M. JOHNSTON, and FALLS B. HERSHEY, St. Louis.

The Implication of Excess Oxygen as a Factor in Cardiac Arrest. SAM E. STEPHENSON, JR., Nashville.

Fat Embolism, Ether Convulsions, and Neurologic Deficits. GUY OWENS and H. WILLIAM SCOTT, JR., Nashville.

Electrical Anesthesia; Some Metabolic Observations and Comparisons. DON MCNEIL, M. DON TURNER, and JAMES D. HARDY, Jackson, Mississippi.

Pulmonary Vascular Changes in Newborn Pups. DAVID D. SNYDER, DUDLEY B. HOULE, and GILBERT S. CAMPBELL, Minneapolis.

Histologic Studies of the Lung During Recovery from Atelectasis. J. RAYMOND HINSHAW and GEORGE L. EMERSON, Rochester, New York.

Isolation of the Elastic Tissue Network of the Lung. ROBERT W. CARTON, BEVERLY TEWS, C. BRUCE TAYLOR, and GEORGE M. HASS, Chicago.

Pulmonary Physiology in the Obese. JOSEF R. SMITH, Jackson, Mississippi.

Hypercholesterolemia and Pulmonary Arteriosclerosis. ERNEST M. BERKAS, DONALD J. FERGUSON, Minneapolis.

Thursday, 8:30 a.m.–12:00 noon.

MYOCARDIAL METABOLISM

Observations on Myocardial Collateral Circulation. E. A. HUSNI and F. A. SIMEONE, Cleveland.

The Systolic and Diastolic Contributions to Coronary Flow. C. WILLIAM HALL, C. FREDERICK KITTLE, and PAUL R. SCHLOERB, Kansas City, Kansas.

Coronary Flow Related to Cardiac Conduction. GEORGE LUMB, R. S. SHACKLET, W. A. DAWKINS, Memphis.

Aortic Flow Pulse Characteristics in Experimental Aortic Insufficiency. CLARENCE S. WELDON and THEODORE COOPER, Bethesda.

Experimental Production of Cardiovascular Anomalies in Dogs Using Trypan Blue. J. HAROLD CONN and JAMES D. HARDY, Jackson, Mississippi.

Metabolism of the Isolated Normothermic and Rewarmed Heart. SAE SOON LEE and W. R. WEBB, Jackson, Mississippi.

A Comparison of Various Techniques for a Safe and Reliable Method of Coronary Arteriography. J. I. FABRIKANT, W. G. ANLYAN, G. J. BAYLIN, and R. B. TRUMBO, Durham.

Relation of Central Depression to Survival from Acute Coronary Occlusion. WILLIAM REGELSON, Buffalo.

The Use of an Intracardiac Pacemaker in the Correction of Total Heart Block. SEYMOUR FURMAN and GEORGE ROBINSON, New York.

Multichamber Pressure Relationships in Experimental Heart Block. NORMAN SIDERIUS, PETER L. BRUNNEN, GEORGE R. DAICOFF, JOSEPH LANCASTER, and PETER V. MOULDER, Chicago.

The Fate of Potassium Used as a Cardioplegic Agent. A. KAPLAN and B. FISHER, Pittsburgh.

High Energy Phosphate Levels in the Myocardium During Various Techniques of Cardiac Arrest as Determined by Cardiac Biopsy. VINCENT L. GOTT, MARILYN M. BARTLETT, and JOHN A. JOHNSON, Minneapolis.

Thursday, 8:30 a.m.–12:00 noon.

NEUROLOGIC SURGERY

The Role of the Adrenal in Intracranial Trauma and Neoplasm. ROBERT G. FISHER and JOHN H. COPENHAVER, JR., Hanover, New Hampshire.

Observations on the Effect of Urea on Cerebrospinal Fluid Pressure in Experimental Animal (Macaque). MANUCHER JAVID and JON ANDERSON, Madison, Wisconsin.

Repeated Loading Tests of the Lumbar Spine. W. G. HARDY, H. R. LISSNER, J. E. WEBSTER, and E. S. GURDJIAN, Detroit.

Confirmation Test of Reaction to Straight Leg Raising. FRANK P. SMITH, Rochester, New York.

Trigeminal Neuralgia Treated with Dilantin. JOSEPH F. DORSEY and RAHAMIN ARAV, Boston.

Globus Pallidus Coagulation Technique. O. J. ANDY and J. S. BROWNE, Jackson, Mississippi.

Ventriculobiliary Shunt—a New Treatment for Hydrocephalus. GEORGE W. SMITH, WILLIAM H. MORETZ, Augusta, Georgia, and WILLIAM PRITCHARD, Bethesda.

The Treatment of Communicating Hydrocephalus by the Absorption of Cerebrospinal Fluid by the Mucosa of an Isolated Segment of Ileum (Modified Ileo-entectropy). CHARLES G. NEUMANN, THOMAS I. HOEN, and DONALD A. DAVIS, New York.

The Effects of Hypothermia on Acute Experimental Subarachnoid Hemorrhage in Dogs. SEAN MULLEN and CHARAS SUWANWELA, Chicago.

Hypothermia and Pial Circulation. L. M. THOMAS, J. E. WEBSTER, and E. S. GURDJIAN, Detroit.

Observations on the Effects of Hypothermia on Experimental Brain Lesions. EDWARD J. LASKOWSKI and IGOR KLATZO, Bethesda.

Application of Positron-Emitting Zirconium-89 for Potential Use in Brain Tumor Localization. JOHN MEALEY, JR., Boston.

Thursday, 1:30–3:00 p.m.

NEUROLOGIC SURGERY

Kinks and Coils in the Cervical Carotid Artery. H. HARVEY GASS, Detroit.

Cortical Veins of the Human Brain. DOGAN M. PERESE, Buffalo.

An Exploration of Factors Involved in the Production and Prevention of Paraplegia Following Intra-aortic Urokon Injection. EDWARD M. LANCE, DUNCAN A. KILLEN, and GUY OWENS, Nashville.

Complications with Hypaque Cerebral Arteriography. J. S. BROWNE and O. J. ANDY, Jackson, Mississippi.

A New Arterial Clamp for External Control of Cerebral Blood Flow; Design and Application. ROBERT J. WHITE, ALFRED UIHLEIN, and JOHN H. GRINDLAY, Rochester, Minnesota.

The Clinical Significance of Variations in the Cervicothoracic and Middle Cervical Ganglia of the Sympathetic Trunk and of Preganglionic Sympathetic Fibers of the Cervical Nerves of Man. RAEBURN C. LLEWELLYN, HOMER D. KIRGIS, and EDWARD McC. PEEBLES, New Orleans.

Thursday, 1:00–3:45 p.m.

GYNECOLOGY AND OBSTETRICS

The Significance of Lactation Induced by Luteotrophin in Women with Metastatic Cancer of the Breast—I, the Effect of Adrenalectomy and Hypophysectomy. THOMAS L. DAO, Buffalo.

The Experimental Study of Chemical and Physical Factors Which May Alter the Radiation Sensitivity of Tumors. JOHN MCLEAN MORRIS and ROBERT K. MODLIN, New Haven, Connecticut.

Postoperative Hysterosalpingography. WILLIAM J. SWEENEY, III, New York.

Steroid Metabolism of the Human Ovary Under Perfusion with Hemoglobin Solution. GEORGE S. RICHARDSON and HOWARD ULFELDER, Boston.

Electrolyte Balance Studies with Antialdersterone Medications. JOHN C. BUCKINGHAM and ALLAN C. BARNES, Cleveland.

The Effect of Oral Estrogen upon the Immediately Postpartum Endometrium and Vaginal Mucosa. C. A. DOUGLAS RINGROSE, Detroit.

Tracheloplasty for Incompetence of the Internal Cervical Os. JOHN ROCK, WILLIAM J. MULLIGAN, and CELSO-RAMON GARCIA, Brookline, Massachusetts.

Comparison of Simultaneously Recorded Electrical Potentials from the Skin and Uterus in Human Labor. EDWARD H. HON and CLARENCE DAVIS, New Haven, Connecticut.

Melanoma and Pregnancy; an Experimental Evaluation of a Clinical Impression. EVERETT C. SHOCKET and JOSEPH G. FORTNER, New York.

A-B-O (H) Blood Group Substances in the Human Maternal-Fetal Barrier and Amniotic Fluid. VINCENT J. FREDA, New York.

Water Equilibration Between the Human Fetus and Mother. HARRY S. MCGAUGHEY, JR., WILLIAM A. SCOGGIN, HERBERT C. JONES, JR., W. NORMAN THORNTON, JR., and W. PARKER ANSLOW, JR., Charlottesville.

Transbuccal Administration of Pitocin. THOMAS F. DILLON, New York.